PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Patient Preferences for Venous Thromboembolism Prophylaxis After Injury: A Discrete Choice Experiment
AUTHORS	Haac, Bryce; O'Hara, Nathan; Mullins, C; Stein, DM; Manson, Theodore; Johal, Herman; Castillo, Renan; O'Toole, Robert; Slobogean, GP

VERSION 1 - REVIEW

REVIEWER	Anneliese M. Schleyer MD Harborview Medical Center, Seattle, Washington, USA
REVIEW RETURNED	14-Mar-2017

GENERAL COMMENTS	A very well written, interesting manuscript - highlighting a very important but infrequently studied topic - pt preferences and trade-off estimates regarding vte prophylaxis. Well done! Thank you for challenging all of us to pursue further research regarding optimal prophylaxis in this high risk population in a pt-centered manner. Well written; methods and analysis well described and performed. Were surveys self-administered? (or interviewer administered?) Study population does not appear to be severely injured (mean ISS 11.7). Did study only include patients with isolated pelvic or acetabular fractures or operative extremity fx (Table 1- pts appear to have primary injury either LE OR UE)? Excluded polytrauma? How is 'primary injury' defined? Did all of these patients - particularly those surveyed as outpatients - discharge to home? if some discharged to SNF, were there differences in preferences based on discharge disposition? (injections may be more/less tolerable if do not need to be self-administered)

REVIEWER	Cheri Walker Southwestern Oklahoma State University College of Pharmacy Weatherford, Oklahoma, USA
REVIEW RETURNED	30-Mar-2017

GENERAL COMMENTS	1. General Comments a. Overall a well-written and clear paper. It is interesting to be able to more objectively assess patient preference between therapy options. b. “Pill” is not appropriate medical terminology. Please

	consider using “tablet” or similar when discussing the results, even if “pill” is left in the patient survey. c. Please consistently add leading zeros before a decimal point (i.e. 0.001 vs .001). 2. Abstract a. Page 2, line 21: please clarify that the patients are adults. 3. Introduction a. Page 4, line 32: do not capitalize “Enoxaparin”. b. Page 4, line 52: please define “CHEST” or give abbreviation previously. 4. Methods a. Explanation of DCEs was clear and helpful. b. Page 6, line 23: how did you determine how long the study should be, or how many patients needed to be included? See STROBE criteria #10. c. Page 7, line 26: did you collect which type of VTE prophylaxis the patient received in actuality, and did this affect the results of their preference? d. Page 7, line 54: it may help readers to clarify that the marginal utility can be positive or negative, with numbers farther from zero indicating more of a preference. e. Page 8, line 8: were age, sex, and race the only variables of interest, or were there others? Please clarify by either removing “e.g.” or adding a clarifier “such as” or “etc”. 5. Results a. Page 8, line 30: please remove the SD after ISS as SD is not listed for the other parameters in the text. b. Page 8, line 52: change “stomach pain and bruising” to “stomach pain or bruising”. 6. Discussion a. Page 10, line 33: change “varies” to “varied”. b. Page 10, line 38: change “risk-benefits” to “risk-benefit”. Also see page 11, line 37. c. Page 10, last paragraph: do the authors have any thoughts as to why females and white ethnicity preferred oral tablets more? d. Page 11, line 21: change “patients’” to “patients”. e. Page 11, line 33-40: long sentence. Consider re-wording or making two sentences. f. Page 11, line 42: remove comma after “studies” to improve readability (clarifies that this is not a list of eras). g. Please add to the discussion the limitation listed after the abstract about “respondent’s actual choices may be different.” 7. Table 1 a. Please define “ASA” in the table footnotes. b. Please briefly explain what the ISS score indicates in the footnotes. 8. Table 2 a. Is the WTP calculated per dose, month, or treatment course? 9. Table 3

	a. Please change the heading of column two to "Acceptable ARR Trade-off" to clarify within the table itself that the values are ARR. 10. Table 4 a. Can the authors clarify why all the WTP values are positive if some of the marginal utilities are negative? Does it mean, for example, that males would be willing to pay $66.79 to take the injection over the pill? Or that they still preferred the oral pill, but less than females?

REVIEWER	Igor Locatelli Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia, EU
REVIEW RETURNED	30-Mar-2017

GENERAL COMMENTS	This article explores the preferences of patients with orthopaedic trauma towards VTE prophylaxis (orally taken ASA or subcutaneously LMWH). The manuscript is in general very fluently written. Abstract: explain the therapy behind oral pills and subcutaneous injections. Abstract: State the patient population in more details. Especially the mean age of the patients should be explicitly stated. Table 2. Explain risk reduction by 1%: is it absolute or relative risk reduction. Be careful with this wording throughout the manuscript. If it is absolute risk reduction (which is more meaningful), then the overall risk of death due to PE should more than 1%, which is very high - please explain this. Methods: DCE is nicely and accurately presented. However, when it comes to multinominal logit model it is not very clear how was the dependent variable used and which independent variables were used. The section in data analysis describing the modelling should be upgraded. Methods: page 8 line 8, please state explicitly what variables of interest were included into the model, not just as e.g…..? Results: The mean age of the patients was 48 years. In terms of VTE complications these are very young patients, so the overall risks for VTE complications are very low. This should be noted under study limitations as this might influence the study results. So, will older patients (e.g aboce 65 years) still prefer peroral against subcutaneous application? Why the age was not included in subgroup analyses (see last paragraph of the results and Table 4) Figure 1. You assumed 0,1% probability for death due to PE. Please provide the reference for this assumption. These estimate seems high, as these patients were young and thus without major CV diseases related comorbidities.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Anneliese M. Schleyer MD
Institution and Country: Harborview Medical Center, Seattle, Washington, USA
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
A very well written, interesting manuscript - highlighting a very important but infrequently studied topic - pt preferences and trade-off estimates regarding vte prophylaxis. Well done! Thank you for challenging all of us to pursue further research regarding optimal prophylaxis in this high risk population in a pt-centered manner.

Well written; methods and analysis well described and performed.

Were surveys self-administered? (or interviewer administered?)

Response: Thank you for your review. The surveys were self-administered. However, a research staff member was available for any questions as the survey was being completed.

Change: Patients were randomly assigned one of the four self-administered surveys. A member of the research staff was available for questions as the study participant completed the survey. (Methods, Study design)

Study population does not appear to be severely injured (mean ISS 11.7).
Did study only include patients with isolated pelvic or acetabular fractures or operative extremity fx (Table 1- pts appear to have primary injury either LE OR UE)? Excluded polytrauma? How is 'primary injury' defined?

Response: Any patient with a pelvic or acetabular fracture, whether it was treated operatively or conservatively, or any operative extremity fracture was eligible for the study. Polytrauma patients were eligible for inclusion in the sample. The primary injury as described in Table 1 refers to the primary orthopaedic injury for the patients. This is the operative or the most severe orthopaedic injury as determined by review of clinical notes. Non-orthopaedic injuries were not accounted for in this variable but are instead accounted for by their contribution to the injury severity score (ISS). The low mean ISS of this sample is likely due many patients having isolated orthopaedic injuries as well as more severely injured patients (e.g. head injury patients) not having the mental capacity needed to complete the DCE survey. Furthermore, ISS scores did range from 4 – 34, however the median (10) interquartile range (8-16) did cluster around our mean value.

Change: "Primary Injury" has been changed to "Primary Orthopaedic Injury" in Table 1.

Change (Discussion): "In the same manner, the mean ISS of our sample was 11.7, likely as a result of many patients having isolated orthopaedic injuries as well as more severely injured patients not having the mental capacity to complete the survey. ISS ranged from 4-34, but there is the possibility that our results may suffer from some respondent bias if trying to extrapolate to a more severely injured population."

Did all of these patients - particularly those surveyed as outpatients - discharge to home? if some discharged to SNF, were there differences in preferences based on discharge disposition? (injections may be more/less tolerable if do not need to be self-administered)

Response: We thank the reviewer for this insightful comment. Not all of these patients were discharged to home. Some patients completed the survey as an inpatient. Others completed the survey during their outpatient visit. To be eligible for the study, the patient required an injury that would result in prophylaxis administration as part of standard of care at our hospital. However, the study participant did not have to be on prophylaxis at the time of the survey. We did not control for discharge disposition in our sample and agree this would be an interesting variable to have included in the analysis. We did include if the survey was administered while the study participant was an inpatient or an outpatient as a covariate in our model. This was found to be significant associated with preferences for a reduced risk of wound complications requiring another surgery.

Change (Discussion): “We were unable to control for patient disposition in our analysis (home vs. rehab), but we did compare responses of inpatients to outpatients.”

Reviewer 2
Reviewer Name: Cheri Walker
Institution and Country: Southwestern Oklahoma State University, College of Pharmacy, Weatherford, Oklahoma, USA
Please state any competing interests or state ‘None declared’: None declared

1. General Comments
a. Overall a well-written and clear paper. It is interesting to be able to more objectively assess patient preference between therapy options.

Response: Thank you for your comments.

b. “Pill” is not appropriate medical terminology. Please consider using “tablet” or similar when discussing the results, even if “pill” is left in the patient survey.

Response/Change: As suggested, we have substituted “tablet” for “pill” throughout the manuscript and tables.

c. Please consistently add leading zeros before a decimal point (i.e. 0.001 vs .001).

Response/Change: Leading zeros have been added prior to all decimal points in the manuscript and tables.

2. Abstract
a. Page 2, line 21: please clarify that the patients are adults.

Response/Change: The word “adult” has been added to the abstract.

3. Introduction
a. Page 4, line 32: do not capitalize “Enoxaparin”.

Response/Change: This has been corrected.

b. Page 4, line 52: please define “CHEST” or give abbreviation previously.

Response/Change: “CHEST” refers to the American College of Chest Physicians. This abbreviation is now noted in the second paragraph of the introduction.

4. Methods
a. Explanation of DCEs was clear and helpful.

b. Page 6, line 23: how did you determine how long the study should be, or how many patients needed to be included? See STROBE criteria #10.

Response: The target sample size for this study was derived by the Rule of Thumb calculation described by Orme and our a priori decision to conduct multiple subgroup analyses. Based on the Rule of Thumb, we calculated that 25 study participants would be required in each possible sub-group category for adequate statistical power. Given known proportions of admission data for this population, a sample size exceeding 200 participants was required to adequately assess heterogeneity in preferences, particularly on sex, race, and health insurance status.

Change: This information has been added to our Methods (study design) section. “The target sample size for this study was derived by the Rule of Thumb calculation described by Orme and our a priori decision to conduct multiple subgroup analyses.31 Based on this calculation,31 we determined that a sample of 25 study participants would be required in each possible sub-group category for adequate statistical power. Given known proportions of admission data for this population, a sample size exceeding 200 participants was required to adequately assess heterogeneity in preferences, particularly on sex, race, and health insurance status.”

c. Page 7, line 26: did you collect which type of VTE prophylaxis the patient received in actuality, and did this affect the results of their preference?

Response: The type of VTE prophylaxis was not collected as part of the study. However, at the time of the study, VTE prophylaxis by low molecular weight heparin was the standard hospital protocol and it is reasonable to assume this was prescribed to all study participants unless there was a contraindication.

d. Page 7, line 54: it may help readers to clarify that the marginal utility can be positive or negative, with numbers farther from zero indicating more of a preference.

Response: We thank the reviewer for this suggestion and added a sentence to the Methods section with this information.

Change: Marginal utility can be positive or negative, with numbers farther from zero indicating a stronger preference.

e. Page 8, line 8: were age, sex, and race the only variables of interest, or were there others? Please clarify by either removing “e.g.” or adding a clarifier “such as” or “etc”.

Response: We have added more detail on the variables that were assessed and how they were coded to our Data Analysis sub-section of the Methods.

Change: Preference heterogeneity was subsequently assessed by adding an interaction term into the model with a priori determined variables of interest. These variables included age (categorized as <40, 40 – 59, >60), sex, race, ASA status (2 vs. >2), the location of primary injury (upper extremity vs. lower extremity), household income (categorized as $20,000, $20,000 - $49,999, $50,000 - $74,999, $75,0000), health insurance status (any vs. none), and the location of recruitment.

5. Results
a. Page 8, line 30: please remove the SD after ISS as SD is not listed for the other parameters in the text.

Response/Change: As requested, the SD for ISS has been removed from the text.

b. Page 8, line 52: change “stomach pain and bruising” to “stomach pain or bruising”.

Response/Change: “Stomach pain and bruising” has been changed to “stomach pain or bruising”.

6. Discussion
a. Page 10, line 33: change “varies” to “varied”.

Response/Change: Changed as requested.

b. Page 10, line 38: change “risk-benefits” to “risk-benefit”. Also see page 11, line 37.

Response/Change: Changed as requested.

c. Page 10, last paragraph: do the authors have any thoughts as to why females and white ethnicity preferred oral tablets more?

Response: We agree that more information on the underlying drivers of this heterogeneity in preferences is required. Unfortunately, we do not have data to gain further insight into these specific variations in preferences nor were we able to find further understanding from the literature that may explain these differences. These tests to explore heterogeneity of preferences were hypothesis generating and will require future investigation

d. Page 11, line 21: change “patients’” to “patients”.

Response/Change: Corrected as suggested.

e. Page 11, line 33-40: long sentence. Consider re-wording or making two sentences.

Response: We thank the reviewer for the suggestion and have separated this into two sentences.

Change: Our study is the first to document the value patients place on various clinically-important outcomes related to VTE prophylaxis. In addition, we define the underlying patient factors that contribute to variation in VTE prophylaxis preferences with risk-benefit tradeoffs among subgroups in this important area of ongoing debate.

f. Page 11, line 42: remove comma after “studies” to improve readability (clarifies that this is not a list of eras).

Response/Change: Removed as suggested.

g. Please add to the discussion the limitation listed after the abstract about “respondent’s actual choices may be different.”

Response: We thank the reviewer for the suggestion and have added this limitation to our Discussion section.

Change: As a result, we are only able to speculate as to why patients valued certain outcomes more than others. In addition, the choice sets were hypothetical scenarios and patient’s actual choices may be different.

7. Table 1
a. Please define “ASA” in the table footnotes.

Response: A notes section has been added to Table 1 to define ASA.

Change: The American Society of Anesthesiologists (ASA) physical status classification system for assessing pre-operative patient fitness.

b. Please briefly explain what the ISS score indicates in the footnotes.

Response: ISS is briefly explained in the Table 1 notes.

Change: Injury Severity Score (ISS) is a well-validated score that assesses trauma severity based on a consensus-derived severity score that classifies each injury from six body regions (head or neck, face, chest, abdomen, extremities, external). A score greater than 15 is commonly referred to as a major trauma (or polytrauma).

8. Table 2
a. Is the WTP calculated per dose, month, or treatment course?

Response: Willingness to pay for the route and side effects category is based on the full treatment course, not per dose. Willingness to pay for all other attributes is based on the incremental change in level.

Change: This information has been added to the Notes section on Table 2.

9. Table 3
a. Please change the heading of column two to “Acceptable ARR Trade-off” to clarify within the table itself that the values are ARR.

Response/Change: As suggested, this has been clarified in the table and defined in the legend and notes.

10. Table 4
a. Can the authors clarify why all the WTP values are positive if some of the marginal utilities are negative? Does it mean, for example, that males would be willing to pay $66.79 to take the injection over the pill? Or that they still preferred the oral pill, but less than females?

Response: All willingness to pay values are presented in reference to a less preferred option. For example, both females and males prefer oral tablets compared to an injection. However, females are willing to pay more for an oral tablet over an injection than males are willing to pay for that same tradeoff (oral tablet over an injection).

Change: Added to the notes section of Table 4. “All willingness to pay values are presented in reference to a less preferred option. For example, both females and males prefer oral tablets compared to an injection. However, females are willing to pay more for an oral tablet over an injection than males are willing to pay for that same tradeoff (oral tablet over an injection). Willingness to pay values for attributes with continuous levels estimate the willingness to pay for an additional 1% absolute reduction in risk.”

Reviewer: 3
Reviewer Name: Igor Locatelli
Institution and Country: Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia, EU
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
This article explores the preferences of patients with orthopaedic trauma towards VTE prophylaxis (orally taken ASA or subcutaneously LMWH). The manuscript is in general very fluently written.

Abstract: explain the therapy behind oral pills and subcutaneous injections.

Response: We thank the reviewing for their suggestion. However, we are concerned the word count limit in the abstract prevents the addition of more detail on the biological rationale behind either venous thromboembolism prophylaxis regimen. We do explain the known patient preference for oral medications over injection medications based on the current literature in the Introduction section.

Abstract: State the patient population in more details. Especially the mean age of the patients should be explicitly stated.

Response: As suggested, we have included more data on the patient population.

Change: 232 adult trauma patients (mean age 47.9 years) with pelvic or acetabular fractures or operative extremity fractures.

Table 2. Explain risk reduction by 1%: is it absolute or relative risk reduction. Be careful with this wording throughout the manuscript. If it is absolute risk reduction (which is more meaningful), then the overall risk of death due to PE should more than 1%, which is very high - please explain this.

Response: We agree with the reviewer that relative vs. absolute is a very important distinction. We have added a sentence in the Table 2 notes to clarify how the levels are presented in this table. Furthermore, we agree that the rate of death due to PE is likely less than 1% for this population. The rate of death due to PE as presented to patients in the DCE scenarios was 0.1 to 0.2%. All attributes with continuous levels are assumed to be linear in this type of analysis. We opted to present all risk level on a common scale (1% absolute risk reduction) for ease in comparison.

Change: All mention of risk reductions has been clarified as absolute risk reductions.

Methods: DCE is nicely and accurately presented. However, when it comes to multinominal logit model it is not very clear how was the dependent variable used and which independent variables were used. The section in data analysis describing the modelling should be upgraded.

Response: In contrast to regression modelling, variables used in a multinomial logit model cannot not simply be described as independent and dependent variables. Multinomial logit modelling is based McFadden's random utility theory, where Xij is an attribute of a choice j that an individual i faces. Therefore, B is the impact of the changes of the attributes and Eij is random component in the following equation.

$Uij = B'xij + Eij$

Suppose that j is selected by the individual i and k is not selected. The equation assumes that the individual i will select j to maximize the random utility function, if and only if $Uij > Uik$. Eij is a random component of the individual utility function. The probability that individual i actually selects j is written as $P(Uij > Uik)$. In the multinomial logit model, a maximum likelihood method is used to estimate the coefficients B in the model below as the marginal utility values for each attribute level.

$Pij = P(Uij > Uik) = \exp(B'Xij) / \exp(B'Xik)$

References:
McFadden D. Econometric models for probabilistic choice among products. Journal of Business. 1980 Jul 1:S13-29.

Louviere JJ, Flynn TN, Carson RT. Discrete choice experiments are not conjoint analysis. J Choice Model 2010;3:57–72.

Change: We have added these two helpful references to the mention of multinomial logit modelling in the data analysis section. It is uncommon to provide this level of modelling detail into a discrete choice experiment manuscript. However, if the reviewers and editor believe this level of detail would be helpful for the reader, we would be willing to add this into the manuscript.

Methods: page 8 line 8, please state explicitly what variables of interest were included into the model, not just as e.g…..?

Response: We have added more detail on the variables that were assessed and how they were coded to our Data Analysis sub-section of the Methods.

Change: Preference heterogeneity was subsequently assessed by adding an interaction term into the model with a priori determined variables of interest. These variables included age (categorized as <40, 40 – 59, >60), sex, race, ASA status (2 vs. >2), the location of primary injury (upper extremity vs. lower extremity), household income (categorized as $20,000, $20,000 - $49,999, $50,000 - $74,999, $75,0000), health insurance status (any vs. none), and the location of recruitment.

Results: The mean age of the patients was 48 years. In terms of VTE complications these are very young patients, so the overall risks for VTE complications are very low. This should be noted under study limitations as this might influence the study results. So, will older patients (e.g above 65 years) still prefer oral against subcutaneous application? Why the age was not included in subgroup analyses (see last paragraph of the results and Table 4)

Response: We appreciate your comment regarding the young mean age of our sample population. The VTE complication risk associated with age is relatively minimal compared to trauma, particularly orthopaedic trauma. Current literature describes the risk of a VTE event without appropriate prophylaxis for orthopaedic trauma to be between 20% - 90%.1-4 As the mean age of our sample is consistent with orthopaedic data from the National Trauma Database, we do not see it as a threat to the external validity of our findings. Furthermore, we did conduct a sub-group analysis using the following age categories (<40, 40 – 59, >60) and found no association between age and the included VTE prophylaxis attributes.

Change: We have added the following clarifying sentence to the end of our Results section, “There were no other significant associations between the tested covariates and our included VTE prophylaxis attributes.”

Figure 1. You assumed 0.1% probability for death due to PE. Please provide the reference for this assumption. These estimate seems high, as these patients were young and thus without major CV diseases related comorbidities.

Response: We recognize that this patient population is young and the majority do not have major cardiovascular disease-related comorbidities. In contrast to diseases like myocardial infarction in which major cardiovascular disease and comorbidities are important risk factors, the strongest risk factors for pulmonary embolism are due to the underlying trauma and not from pre-existing comorbidities. Pulmonary embolism is the third most common cause of death in patients who survive the first 24 hours following injury.

Related References from Manuscript:
1. Shackford SR, Moser KM. Deep venous thrombosis and pulmonary embolism in trauma patients. J Intensive Care Med. 1988; 3(2):87-98.
2. Geerts WH, Code KI, Jay RM, et al. A prospective study of venous thromboembolism after major trauma. N Engl J Med. 1994;331(24):1601–1606.
3. O'Malley KF, Ross SE. Pulmonary embolism in major trauma patients. J Trauma. 1990;30(6):748–750.
4. Sevitt S, Gallagher N. Venous thrombosis and pulmonary embolism. A clinico-pathological study in injured and burned patients. Br J Surg. 1961;48:475–489.

VERSION 2 – REVIEW

REVIEWER	Cheri Walker Southwestern Oklahoma State University, College of Pharmacy, Weatherford, Oklahoma, USA
REVIEW RETURNED	01-May-2017

GENERAL COMMENTS	1. General Comments a. Authors adequately addressed the reviewers' comments. Paper is improved and clarified with the adjustments. 2. Introduction a. Page 4, line 37: change "ASA" to "aspirin". ASA is not used to abbreviate acetylsalicylic acid again, but it is used to abbreviate American Society of Anesthesiologists. 3. Methods a. The authors responded to my comment in the first revision, and I feel that adding this response to the manuscript would be of benefit to the readers. "Page 7, line 26: did you collect which type of VTE prophylaxis the patient received in actuality, and did this affect the results of their preference? Response: The type of VTE prophylaxis was not collected as part of the study. However, at the time of the study, VTE prophylaxis by low molecular weight heparin was the standard hospital protocol and it is reasonable to assume this was prescribed to all study participants unless there was a contraindication."

REVIEWER	Igor Locatelli Faculty of Pharmacy University of Ljubljana
REVIEW RETURNED	01-May-2017

GENERAL COMMENTS	1. Abstract: explain the therapy behind oral pills and subcutaneous injections. Response: We thank the reviewing for their suggestion. However, we are concerned the word count limit in the abstract prevents the addition of more detail on the biological rationale behind either venous thromboembolism prophylaxis regimen. We do explain the known patient preference for oral medications over injection medications based on the current literature in the Introduction section. Reviewer: OK I agree in the part of not changing the abstract. However, the readers of the BMJ journal would be interested in what drug option had you have in mind when setting oral vs. subcutaneous application. You clearly mentioned enoxaparin for subcutaneous application, however, for the oral part, it is not clear which drug is taken into account. This is important or even crucial as the DCE was based on efficacy and drug safety as well. In the manuscript acetylsalicylic acid only was mentioned in the introduction as possible therapy, but overall it is not clear if

	acetylsalicylic acid was supposed as “oral tablet”. What about warfarin, and more importantly new oral anticoagulants? So, the part regarding the drugs behind the oral therapy should be clearly stated (not necesarly in the abstract) and if only ASA was considered there should be a discussion regarding other possible oral therapies. You still have some terminology flaws: - In the manuscript you have ASA defined in two ways: as acetylsalicylic acid and as American Society of Anesthesiologists. - Oral tablet vs. injection. This is still patient wording. It will be much more “scientifically correct” if you use oral vs. subcutaneous application. 2. Table 2. Explain risk reduction by 1%: is it absolute or relative risk reduction. Be careful with this wording throughout the manuscript. If it is absolute risk reduction (which is more meaningful), then the overall risk of death due to PE should more than 1%, which is very high - please explain this. Response: We agree with the reviewer that relative vs. absolute is a very important distinction. We have added a sentence in the Table 2 notes to clarify how the levels are presented in this table. Furthermore, we agree that the rate of death due to PE is likely less than 1% for this population. The rate of death due to PE as presented to patients in the DCE scenarios was 0.1 to 0.2%. All attributes with continuous levels are assumed to be linear in this type of analysis. We opted to present all risk level on a common scale (1% absolute risk reduction) for ease in comparison. Change: All mention of risk reductions has been clarified as absolute risk reductions. Reviewer: I agree with the change. I can imagine your extrapolation. Calculating WTP for 1% absolute risk reduction for death for PE in these patients, is like calculating WTP for 1 ton of weight reduction if patient weight was an influencing factor. 3. Methods: DCE is nicely and accurately presented. However, when it comes to multinominal logit model it is not very clear how was the dependent variable used and which independent variables were used. The section in data analysis describing the modelling should be upgraded. Change: We have added these two helpful references to the mention of multinomial logit modelling in the data analysis section. It is uncommon to provide this level of modelling detail into a discrete choice experiment manuscript. However, if the reviewers and editor believe this level of detail would be helpful for the reader, we would be willing to add this into the manuscript. Reviewer: There is no need for further explanation. I have no further comments on other comments

VERSION 2 – AUTHOR RESPONSE

Reviewer 2
Reviewer Name: Cheri Walker

Institution and Country: Southwestern Oklahoma State University, College of Pharmacy, Weatherford, Oklahoma, USA
Please state any competing interests or state 'None declared': None declared

1. General Comments
a. Authors adequately addressed the reviewers' comments. Paper is improved and clarified with the adjustments.

2. Introduction
a. Page 4, line 37: change "ASA" to "aspirin". ASA is not used to abbreviate acetylsalicylic acid again, but it is used to abbreviate American Society of Anesthesiologists.

Response: Thank you for pointing this out. We have changed ASA to aspirin on page 4, line 37.

3. Methods
a. The authors responded to my comment in the first revision, and I feel that adding this response to the manuscript would be of benefit to the readers. "Page 7, line 26: did you collect which type of VTE prophylaxis the patient received in actuality, and did this affect the results of their preference? Response: The type of VTE prophylaxis was not collected as part of the study. However, at the time of the study, VTE prophylaxis by low molecular weight heparin was the standard hospital protocol and it is reasonable to assume this was prescribed to all study participants unless there was a contraindication."

Response: We agree that adding this explanation would benefit readers and have added it to the methods study design section on page 7.

Change (page 7): The type of VTE prophylaxis was not collected as part of the study. However, at the time of the study, VTE prophylaxis by LMWH was the standard hospital protocol and it is reasonable to assume this was prescribed to all study participants unless there was a contraindication.

Reviewer: 3
Reviewer Name: Igor Locatelli
Institution and Country: Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia, EU
Please state any competing interests or state 'None declared': None declared

1. Abstract: explain the therapy behind oral pills and subcutaneous injections.

Response: We thank the reviewing for their suggestion. However, we are concerned the word count limit in the abstract prevents the addition of more detail on the biological rationale behind either venous thromboembolism prophylaxis regimen. We do explain the known patient preference for oral medications over injection medications based on the current literature in the Introduction section.

Reviewer: OK I agree in the part of not changing the abstract.
However, the readers of the BMJ journal would be interested in what drug option had you have in mind when setting oral vs. subcutaneous application. You clearly mentioned enoxaparin for subcutaneous application, however, for the oral part, it is not clear which drug is taken into account. This is important or even crucial as the DCE was based on efficacy and drug safety as well. In the manuscript acetylsalicylic acid only was mentioned in the introduction as possible therapy, but overall it is not clear if acetylsalicylic acid was supposed as "oral tablet". What about warfarin, and more importantly new oral anticoagulants?

So, the part regarding the drugs behind the oral therapy should be clearly stated (not necesarly in the abstract) and if only ASA was considered there should be a discussion regarding other possible oral therapies.

Response: We have clarified in the introduction (page 4) that aspirin is the oral tablet that the discrete choice experiement was based on. Typically the other oral anticoagulants are used for therapeutic anticoagulation and not for prevention. For this reason we chose to base our choices for an oral tablet on aspirin because it is the most commonly used alternative to low molecular weight heparin for venous thromboembolism prophylaxis in orthopaedic trauma. We have added an explanation for why attributes were based on aspirin and not other oral anticoagulants to the methods study design section on page 7.

Change (page 7): “Values for these attributes were based on available literature and clinical experience with two commonly prescribed VTE prophylaxis medications in this population: LMWH (a subcutaneous injection) and aspirin (an oral tablet). Attributes were not reflective of other oral anticoagulants because those medications are typically used for treatment of VTE events rather than prevention, and the focus of this DCE is preferences for prophylaxis administered to prevent VTE events.”

You still have some terminology flaws:

- In the manuscript you have ASA defined in two ways: as acetylsalicylic acid and as American Society of Anesthesiologists.

Response: Thank you for pointing this out. We have edited the manuscript as per our response to Reviewer 2 so that ASA only refers to American Society of Anesthesiologists.

- Oral tablet vs. injection. This is still patient wording. It will be much more “scientifically correct” if you use oral vs. subcutaneous application.

Response: We have edited the manuscript so that all mentions of an injection clarify that the injection is subcutaneous.

2. Table 2. Explain risk reduction by 1%: is it absolute or relative risk reduction. Be careful with this wording throughout the manuscript. If it is absolute risk reduction (which is more meaningful), then the overall risk of death due to PE should more than 1%, which is very high - please explain this.

Response: We agree with the reviewer that relative vs. absolute is a very important distinction. We have added a sentence in the Table 2 notes to clarify how the levels are presented in this table. Furthermore, we agree that the rate of death due to PE is likely less than 1% for this population. The rate of death due to PE as presented to patients in the DCE scenarios was 0.1 to 0.2%. All attributes with continuous levels are assumed to be linear in this type of analysis. We opted to present all risk level on a common scale (1% absolute risk reduction) for ease in comparison.

Change: All mention of risk reductions has been clarified as absolute risk reductions.

Reviewer: I agree with the change. I can imagine your extrapolation. Calculating WTP for 1% absolute risk reduction for death for PE in these patients, is like calculating WTP for 1 ton of weight reduction if patient weight was an influencing factor.

3. Methods: DCE is nicely and accurately presented. However, when it comes to multinominal logit model it is not very clear how was the dependent variable used and which independent variables were used. The section in data analysis describing the modelling should be upgraded.

Change: We have added these two helpful references to the mention of multinomial logit modelling in the data analysis section. It is uncommon to provide this level of modelling detail into a discrete choice experiment manuscript. However, if the reviewers and editor believe this level of detail would be helpful for the reader, we would be willing to add this into the manuscript.

Reviewer: There is no need for further explanation.

I have no further comments on other comments