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Patient Preferences for Venous Thromboembolism Prophylaxis After Injury: A Discrete Choice Experiment

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Abstract

Objective: Limited evidence for the optimal venous thromboembolism (VTE) prophylaxis regimen in orthopaedic trauma leads to variability in regimens. We sought to delineate patient preferences towards cost, complication profile, and administration route.

Design: Discrete choice experiment (DCE).

Setting: Level 1 trauma center in Baltimore, USA.

Participants: 232 patients with pelvic or acetabular fractures or operative extremity fractures.

Primary and secondary outcome measures: Relative preferences and trade-off estimates for a 1% reduction in complications were estimated using multinomial logit modelling. Interaction terms were added to the model to assess heterogeneity in preferences.

Results: Patients preferred oral pills over subcutaneous injections (marginal utility, 0.16; 95% CI: 0.11 - 0.21, $P<.0001$). Preferences changed in favor of injections with an absolute risk reduction of 6.98% in bleeding, 4.53% in wound complications requiring reoperation, 1.27% in VTE, and 0.07% in death from pulmonary embolism (PE). Patient characteristics (sex, race, type of injury, time since injury) affected patient preferences ($P<.01$).

Conclusions: Patients preferred oral prophylaxis and were most concerned about risk of death from PE. Furthermore, the findings estimated the trade-offs acceptable to patients and heterogeneity in preferences for VTE prophylaxis.

Strengths and limitations of this study:

- This study quantifies patient preferences for venous thromboembolism prophylaxis in a high risk, and often difficult to research, population.
- The results provide valuable benefit-risk tradeoffs estimates to guide clinicians in a common decisional dilemma.
- High face validity in the choice sets is demonstrated by the directionality, magnitude, and consistency of the responses.
- The high response rate captured in this prospective study reduces response bias present in other survey methods.
- The choice sets presented to respondents were hypothetical scenarios, and the respondent's actual choices may be different.

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Introduction

Traumatic injury is a well-described risk factor for the development of venous thromboembolism (VTE). The incidence of VTE among trauma patients ranges from 20 to 90% without any preventative measure.[1] In addition, pulmonary embolism (PE) is the third most common cause of death in patients who survive the first 24 hours following injury.[1-4] Orthopaedic trauma patients in particular have several well-known risk factors for VTE placing them at exceptionally high risk.[2, 5-8] Fortunately, chemoprophylaxis has been shown to significantly reduce the incidence of VTE in this population.[9] However controversy exists as to the optimal VTE prophylaxis regimen in orthopaedic trauma patients.[10-15]

For many orthopaedic populations, the American College of Chest Physicians and the Eastern Association for the Surgery of Trauma recommend Enoxaparin (low molecular weight heparin (LMWH)) by subcutaneous injection for VTE prophylaxis, but recent studies show that oral acetylsalicylic acid (ASA) may be an equally effective alternative with lower risk of bleeding complications.[10-15] However, only limited data is available specific to orthopaedic trauma patients who may have even higher risk for both VTE events and bleeding.[16] The Orthopaedic Trauma Association Evidence Based Quality Value and Safety Committee highlights variability in prescribed regimens due to the poor scientific support for various regimens and emphasizes the need for guidelines to improve patient care.[17]

The CHEST guidelines emphasize the need for systematic reviews of patient values and preferences when creating guidelines for specific populations.[18] Creation of guidelines requires making risk and benefit trade-offs, and patient values regarding VTE prophylaxis depend on the

health outcomes considered. Furthermore, defining the heterogeneity of preferences in this patient population is necessary to provide valuable individualized VTE prevention options. Implementing guidelines that consider patient preferences may increase patient satisfaction with and improve adherence to clinical treatments.[28] Patient medication refusal is a leading cause of non-administration of VTE prophylaxis in inpatients, and missed doses are highly associated with increased VTE incidence.[19-21] In a study of medical and surgical patient preferences for VTE prophylaxis regimens, the majority of patients preferred oral administration over subcutaneous injection if all other factors were equal.[22] Patients who preferred subcutaneous administration presumed a faster onset of action and were less likely to refuse administration.

Existing VTE prevention studies do not evaluate patient preferences, investigate acceptable trade-offs of the risks and benefits of those medications, or determine heterogeneity in preferences based on demographic and clinical characteristics. The purpose of this study was to elicit the preferences of orthopaedic trauma patients towards currently available VTE prophylaxis, examine acceptable tradeoffs of the potential complications related to those medications, and determine heterogeneity in preferences among patient subgroups.

Methods

A discrete choice experiment (DCE) was prospectively administered to orthopaedic trauma patients at a level-1 trauma center. DCEs are a quantitative technique used to measure individual preferences in a variety of health care settings by administering surveys that ask individuals to choose the best option between two or more hypothetical scenarios, or choice sets.[23-24,29] Options are described with a fixed set of attributes levels that vary in each scenario. The data collected

can be used to assess the relative importance of each attribute and acceptable trade-offs among attributes. Monetary costs can be included to produce willingness-to-pay estimates.

Study setting and population

This study was conducted at the R Adams Cowley Shock Trauma Center in Baltimore, Maryland and received prior approval by the Institutional Review Board at the University of Maryland School of Medicine. All adult (≥ 18 years) patients treated with pelvic or acetabular fractures or an operative extremity fracture were assessed for eligibility from November 2015 through February 2016. Patients who were unable to consent due to intubation or altered mental status and non-English speaking patients were excluded. Upon written consent, patients were enrolled in the study as inpatients or at an outpatient follow-up appointment within 4 months from their initial admission for their injury.

Study design

The attributes and their corresponding levels were selected based on a literature review, patient interviews, expert consultation, and a retrospective review of patient outcomes. Medication attributes used in the DCE included medication administration route (oral pill vs. needle injection), cost, possible side effects including bruising and stomach pain, risk of having a bleeding complication that requires a blood transfusion, risk of having a wound complication that requires another operation, risk of VTE requiring therapeutic anticoagulation for 6 months, and risk of death due to PE. These attributes were chosen to reflect medication qualities that patients

are aware of when taking medications (route, cost, side effects) and clinically-important outcomes.

Forty choice sets were developed using a Bayesian D-optimal design with JMP Version 12 software (SAS Institute, Cary, NC) to ensure maximum variation in attribute comparison. The 40 choice sets were then randomly divided into four surveys, each with 10 choice sets, to minimize respondent burden. As documented by Sandor et al,[30] using heterogeneous designs produce substantial improvements in efficiency over a single survey and provides more precision in estimating true parameters. Each choice set compared two hypothetical VTE prophylaxis medications described by their attributes (**Figure 1**). Patients were randomly administered one of the four surveys. Demographic data including age, sex, race (as defined by the participant), type of injury, Injury Severity Score, American Society of Anesthesiologists (ASA) physical status, income, health insurance status, days on prophylaxis, and timing of recruitment (inpatient vs. outpatient) was collected from both the survey and the medical record.

Data Analysis

Data collected through the DCE survey allows the quantification of and statistical inference about the relative importance of VTE prophylaxis medication attributes. A multinomial logit model, with effects coding, was used to estimate patient preferences using marginal utility, willingness-to-pay, and acceptable trade-off estimates for a 1% reduction in VTE complications or side effects. Marginal utility is a measure of patient preference, with the estimate signifying the strength and direction of one's preference towards the attribute. With this analysis, we are able to determine the relative magnitude of patient preferences to avoid VTE-related

complications in association with their medication choice. Preference heterogeneity was subsequently assessed by adding an interaction term into the model with a priori determined variables of interest (e.g. age, sex, or race). All data analysis was conducted using the Choice Modeling platform in JMP Version 12.

Results

Of the 310 patients screened for participation, 50 were ineligible (40 unable to consent due to altered mental status, 8 non-English speaking, 2 contraindicated for VTE prophylaxis) and 28 (11%) patients refused participation. Of the 232 patients included in the analysis, the mean age was 47.9 years, with 56.9% male, and 66.8% were white. The majority of participants had a lower extremity injury (83.6%), with a mean injury severity score of 11.7 (SD, 6.7), and were fully insured (83.1%) (**Table 1**).

Patients most strongly preferred a reduction in risk of death by PE (marginal utility, 4.57; $P<.0001$), distantly followed by a reduction in the risk of VTE requiring therapeutic anticoagulation, wound complications requiring another surgery, and bleeding complications requiring a transfusion (**Table 2**). Patients were willing to pay $1686.90 for a 1% reduction in risk of death due to PE compared to $92.29 or less for a 1% reduction in any of the other measured outcome variables. Patients also preferred to take oral pills (marginal utility, 0.16; $P<.0001$) and were willing to pay $117.45 to receive prophylaxis via oral route over subcutaneous injection. Possible medication side effects, such as stomach pain and bruising, did not significantly influence patient preferences ($P>.1$).

To change patient preference in favor of injections requires a 6.98% absolute reduction in the risk of bleeding complications requiring transfusion, a 4.53% absolute reduction in the risk of wound complications requiring reoperation, and a 1.27% absolute reduction in risk of VTE requiring therapeutic anticoagulation (**Table 3**). In contrast, only a 0.07% absolute reduction in risk of death due to PE was needed to change patient preference.

In our subgroup analyses examining heterogeneity in preferences, patients who were female, white, or had lower extremity injuries demonstrated significantly stronger preference for oral VTE prophylaxis over subcutaneous injections ($P<.05$) (**Table 4**). Patients with upper extremity injuries valued a reduction in risk of bleeding complications more than patients with lower extremity injuries ($P=.01$). Patients who were recruited as an inpatient valued a reduction in risk of wound complications requiring reoperation more than patients who were recruited from the outpatient clinic ($P<.01$).

Discussion

Consistent with previous studies,[22] our study demonstrates a strong patient preference for oral VTE prophylaxis over subcutaneous injection when all other relevant attributes are equal. However, patients only required a small reduction in the absolute risk of death due to PE to change their preference in favor of an injection. When choosing between VTE prophylaxis regimens, patients most valued (in order): risk of death due to PE, risk of VTE requiring therapeutic anticoagulation, risk of wound complications requiring reoperation, and risk of bleeding complications requiring transfusion. A defined reduction in any of these outcomes could change patient preference to favor the injection route. In addition, underlying patient

factors such as sex, race, type of injury, and inpatient status led to significant heterogeneity in patient preferences.

To our knowledge, our study is the first to assess the weight of patient-valued outcomes regarding potential risks and complications of VTE prophylaxis. The study also determined patient characteristics associated with heterogeneity in their preferences. Previous studies have shown that patient refusal is a common reason for missed VTE doses and increases the risk of a VTE event.[19-22] Patient preference for oral medications is also well-documented.[22,25] Our study also demonstrates a strong preference for oral medications, but our results show that this preference can change if the risk of the aforementioned patient-important outcomes is high enough. Patients were particularly concerned about the risk of death due to PE, requiring only a 0.07% absolute reduction in risk of death to change patient preference in favor of an injection. In addition, only relatively small reductions in the risk of other outcomes were required to change patient preference. Furthermore, the preference for route varies significantly depending on the patient's sex, race, type of injury, and inpatient status.

While the design of the DCE enables the assessment of risk-benefits tradeoffs among subgroups, it does not allow for qualitative analysis of patient preferences. As a result, we are only able to speculate as to why patients valued certain outcomes more than others. The greater value placed on risk of death due to PE compared to other outcome measures could be a result of death being the easiest outcome variable for the average patient to understand. Patients who were recruited as an inpatient were more concerned about the risk of reoperation than patients recruited as outpatients, potentially because their injury and initial operation were more recent in their memory. In addition, study participants had varying lengths of VTE prophylaxis prescribed at time of recruitment and some patients were closer to time of injury and initial operation than

others. Although, when assessed, time since injury did not affect patient preferences. Some participants had personal experience with one of the measured outcomes while others had no history of complications, which we were unable to control for in our final analysis. Lastly, we did not collect data on patient education level which could affect the patient's understanding of certain outcomes, however income and insurance level may be surrogate markers for education and were included in the analysis.

In the current era of patient-centered healthcare, it is important that we consider all outcomes that patients' value and the heterogeneity in those preferences when conducting clinical comparative effectiveness research and when making clinical guidelines in order to improve healthcare delivery and reduce cost.[26, 27,28] Our data demonstrate that orthopaedic trauma patients prefer VTE prophylaxis by oral pill to prophylaxis by subcutaneous injection when all other relevant attributes are equal. However, the risk of death due to PE is the dominant concern when choosing a regimen. Our study is the first to document the value patients place on various clinically-important outcomes related to VTE prophylaxis and to define the underlying patient factors that contribute to variation in VTE prophylaxis preferences with risk-benefits tradeoffs among subgroups in this important area of ongoing debate. In the era of patient-centered healthcare, future studies, and clinical guideline recommendations comparing available VTE prophylaxis regimens should focus on the outcomes most important to patients and incorporate patient trade-off estimates to ensure their work is reflective of patient preferences.

Table 1 Characteristics of orthopaedic fracture participants (n=232)

Characteristic	Mean (SD)
Male, No. (%)	132 (56.9)
Age, y	47.9 (17.7)
Race, No. (%)	
White	155 (66.8)
Black	62 (26.7)
Other	8 (3.4)
Hispanic	7 (3.0)
Primary Injury, No. (%)	
Lower Extremity	194 (83.6)
Upper Extremity	38 (16.4)
ASA, No. (%)	
1	21 (9.1)
2	117 (50.4)
3	81 (34.9)
4	11 (4.7)
Unknown	2 (0.9)
Injury severity score	11.7 (6.7)
Income, $USD, No. (%)	
<$10,000	46 (19.8)
$10,000 - $19,999	20 (8.6)
$20,000 - $34,999	35 (15.1)
$35,000-$49,999	24 (10.3)
$50,000 -$74,999	26 (11.1)
$75,000 - $100,000	24 (10.3)
>$100,000	35 (15.1)
Unknown	22 (9.5)
Health Insurance, No. (%)	
Fully Insured	193 (83.1)
Partially Insured	12 (5.2)
Uninsured	24 (10.3)
Unknown	3 (1.3)
Timing of recruitment No. (%)	
In-patient	78 (33.6)
Out-patient	154 (66.4)

Table 2 Patient preferences and valuation of venous thromboembolism prophylaxis attributes

Attribute	Level	Marginal Utility	95% CI	WTP	*P* Value
Route	Oral pill	0.16	0.11 - 0.21	$117.45	<.0001
	Injection	-0.16	-0.21 – -0.11	-	-
Side Effects	Bruising on leg	-0.04	-0.11 – 0.02	-$45.94	0.11
	Stomach pain	-0.04	-0.12 – 0.04	-$44.08	-
	No side effects	0.08	0.003 – 0.16	$45.08	-
Bleeding complications requiring transfusion	Reduce risk by 1%	0.05	0.04 – 0.05	$16.83	<0.0001
Wound complications requiring another surgery	Reduce risk by 1%	0.07	0.06 – 0.08	$25.91	<0.0001
Blood clot requiring long-term medication	Reduce risk by 1%	0.25	0.15 – 0.36	$92.29	<0.0001
Death due to PE	Reduce risk by 1%	4.57	3.26 – 5.89	$1686.90	<0.0001
Cost	$10 increase	-0.03	-0.04 – -0.02	Reference	<0.0001

PE = pulmonary embolism; CI = confidence interval; WTP = willingness to pay

Note: Marginal utility quantifies the additional satisfaction gained by the patient for each described attribute/level. Negative marginal utility values signify an aversion to or dissatisfaction with the described attribute/level.

Table 3 The absolute risk reduction of a potential complication that a patient would be willing to accept to change their route preference from oral to injection prophylaxis

Attribute	Acceptable Trade-off
Bleeding complications requiring transfusion	6.98%
Wound complications requiring another surgery	4.53%
Blood clot requiring long-term medication	1.27%
Death due to PE	0.07%

PE = pulmonary embolism

Table 4 Sub-group analysis quantifying heterogeneity in patient preferences

Attribute	Level	Sub-Group	Marginal Utility	95% CI	WTP	*P* Value
Route	Take oral pill over injection	Sex [Female]	0.07	0.02 – 0.11	$201.24	<0.01
		Sex [Male]	-0.07	-0.11 - -0.02	$66.79	
		Race [White]	0.09	0.03 – 0.14	$182.23	<0.01
		Race [Black]	-0.09	-0.14 - -0.03	$18.48	
		Injury [Lower Extremity]	0.08	0.02 – 0.15	$132.38	0.01
		Injury [Upper Extremity]	-0.08	-0.15 - -0.02	$18.98	
Bleeding complications requiring transfusion	Reduce risk by 1%	Injury [Lower Extremity]	-0.02	-0.03 - -0.003	$14.50	0.01
		Injury [Upper Extremity]	0.02	0.003 – 0.03	$32.04	
Wound complications requiring another surgery	Reduce risk by 1%	Recruitment [In-patient]	0.02	0.003 – 0.03	$46.32	<0.01
		Recruitment [Out-patient]	-0.02	-0.03 – -0.003	$20.24	

CI = confidence interval; WTP = willingness to pay

Note: Marginal utility quantifies the additional satisfaction gained by the patient for each described attribute/level. Negative marginal utility values signify an aversion to or dissatisfaction with the described attribute/level.

Figure 1: Sample question from the discrete choice experiment survey administered to participants. In each question the values for each hypothetical medication are varied.

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Author Contribution

BH contributed to the literature search, study design, data collection, data interpretation, writing, and critical revision. NNO contributed to the literature search, study design, data analysis, data interpretation, writing, and critical revision. CDMcontributed to the data interpretation and critical revision. DS, TTM, HJ, RVO, and GPS contributed to the literature search, study design, data interpretation, and critical revision. RC contributed to the study design, data analysis, data interpretation, and critical revision. All authors have approved the final version of the article submitted and agree to be accountable for all aspects of the work.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in

the submitted work in the previous three years other than those listed below; no other relationships or activities that could appear to have influenced the submitted work apart from the following:

Dr. Mullins reports consulting with Bayer, Daiichi Sankyo, Janssen/J&J, Mundipharma, Novo Nordisk, and Pfizer and receiving grants from Bayer, Novartis, Merck, and Pfizer. Dr. Stein reports receiving grants from the US Air Force and serves as an advisor for Decisio Health, Inc. Dr. Manson reports consulting with Stryker, Globus, and Smith & Nephew, being paid for expert testimony from various law firms, and payment for lectures by the Maine Review Course. Dr. O'Toole reports consulting with Coorstek (Zimmer) and Smith & Nephew and receiving royalties from Coorstek. Dr. Slobogean reports payments for presenting by Zimmer Biomet. No other disclosures were reported.

Data sharing statement

No additional data are available.

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Which medication would you prefer?

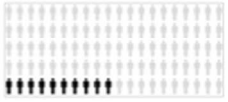
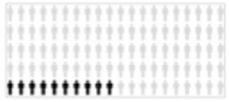
	Medication A		Medication B
Type of daily medication	Oral pill		Needle injection
What will it **cost** you	$100		$50
Possible **side effect**	None		Bruising on leg
Chance that you will have a bleeding complication and need a **blood transfusion**	10 out of 1000		100 out of 1000 
Chance that you will have wound complication and need **another operation**	50 out of 1000 		100 out of 1000 
Chance that you will have a blood clot and have to take **medications for 6 months**	20 out of 1000 		10 out of 1000
Chance of **death** due to a pulmonary embolism	1 out of 1000		1 out of 1000
Check one	Prefer **Medication A** ☐		Prefer **Medication B** ☐

Figure 1. Sample question from the discrete choice experiment survey administered to participants. In each question the values for each hypothetical medication are varied.

172x209mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page 1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Page 4-5**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page 5**
Methods		
Study design	4	Present key elements of study design early in the paper **Page 5-6**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 6**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants **Page 6**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page 6-7**
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 **Page 7**
Bias	9	Describe any efforts to address potential sources of bias **Page 7-8**
Study size	10	Explain how the study size was arrived at **Page 7**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **Page 7-8**
		(*b*) Describe any methods used to examine subgroups and interactions **Page 7-8**
		(*c*) Explain how missing data were addressed **Page 7-8**
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses **Page 7-8**
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 **Page 8**
		(b) Give reasons for non-participation at each stage **Page 8**
		(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 **Page 8**
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures **Page 8**
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 **Page 9**
		(*b*) Report category boundaries when continuous variables were categorized **Page 9**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a

		meaningful time period
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Discussion		
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Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Page 11**
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Other information		
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*Give information separately for exposed and unexposed groups.

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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Patient Preferences for Venous Thromboembolism Prophylaxis After Injury: A Discrete Choice Experiment

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Patient Preferences for Venous Thromboembolism Prophylaxis After Injury: A Discrete Choice Experiment

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Abstract

Objective: Limited evidence for the optimal venous thromboembolism (VTE) prophylaxis regimen in orthopaedic trauma leads to variability in regimens. We sought to delineate patient preferences towards cost, complication profile, and administration route (oral tablet vs. subcutaneous injection).

Design: Discrete choice experiment (DCE).

Setting: Level 1 trauma center in Baltimore, USA.

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

Primary and secondary outcome measures: Relative preferences and trade-off estimates for a 1% reduction in complications were estimated using multinomial logit modelling. Interaction terms were added to the model to assess heterogeneity in preferences.

Results: Patients preferred oral tablets over subcutaneous injections (marginal utility, 0.16; 95% CI: 0.11 - 0.21, $P<0.0001$). Preferences changed in favor of injections with an absolute risk reduction of 6.98% in bleeding, 4.53% in wound complications requiring reoperation, 1.27% in VTE, and 0.07% in death from pulmonary embolism (PE). Patient characteristics (sex, race, type of injury, time since injury) affected patient preferences ($P<0.01$).

Conclusions: Patients preferred oral prophylaxis and were most concerned about risk of death from PE. Furthermore, the findings estimated the trade-offs acceptable to patients and heterogeneity in preferences for VTE prophylaxis.

Strengths and limitations of this study:

- This study quantifies patient preferences for venous thromboembolism prophylaxis in a high risk, and often difficult to research, population.
- The results provide valuable benefit-risk tradeoffs estimates to guide clinicians in a common decisional dilemma.
- High face validity in the choice sets is demonstrated by the directionality, magnitude, and consistency of the responses.
- The high response rate captured in this prospective study reduces response bias present in other survey methods.
- The choice sets presented to respondents were hypothetical scenarios, and the respondent's actual choices may be different.

Manuscript Text (Word Count: 2349)

Introduction

Traumatic injury is a well-described risk factor for the development of venous thromboembolism (VTE). The incidence of VTE among trauma patients ranges from 20 to 90% without any preventative measure.[1] In addition, pulmonary embolism (PE) is the third most common cause of death in patients who survive the first 24 hours following injury.[1-4] Orthopaedic trauma patients in particular have several well-known risk factors for VTE placing them at exceptionally high risk.[2, 5-8] Fortunately, chemoprophylaxis has been shown to significantly reduce the incidence of VTE in this population.[9] However controversy exists as to the optimal VTE prophylaxis regimen in orthopaedic trauma patients.[10-15]

For many orthopaedic populations, the American College of Chest Physicians (CHEST) and the Eastern Association for the Surgery of Trauma recommend enoxaparin (low molecular weight heparin (LMWH)) by subcutaneous injection for VTE prophylaxis, but recent studies show that oral acetylsalicylic acid (ASA) may be an equally effective alternative with lower risk of bleeding complications.[10-15] However, only limited data is available specific to orthopaedic trauma patients who may have even higher risk for both VTE events and bleeding.[16] The Orthopaedic Trauma Association Evidence Based Quality Value and Safety Committee highlights variability in prescribed regimens due to the poor scientific support for various regimens and emphasizes the need for guidelines to improve patient care.[17]

The CHEST guidelines emphasize the need for systematic reviews of patient values and preferences when creating guidelines for specific populations.[18] Creation of guidelines requires making risk and benefit trade-offs, and patient values regarding VTE prophylaxis depend on the

health outcomes considered. Furthermore, defining the heterogeneity of preferences in this patient population is necessary to provide valuable individualized VTE prevention options. Implementing guidelines that consider patient preferences may increase patient satisfaction with and improve adherence to clinical treatments.[28] Patient medication refusal is a leading cause of non-administration of VTE prophylaxis in inpatients, and missed doses are highly associated with increased VTE incidence.[19-21] In a study of medical and surgical patient preferences for VTE prophylaxis regimens, the majority of patients preferred oral administration over subcutaneous injection if all other factors were equal.[22] Patients who preferred subcutaneous administration presumed a faster onset of action and were less likely to refuse administration.

Existing VTE prevention studies do not evaluate patient preferences, investigate acceptable trade-offs of the risks and benefits of those medications, or determine heterogeneity in preferences based on demographic and clinical characteristics. The purpose of this study was to elicit the preferences of orthopaedic trauma patients towards currently available VTE prophylaxis, examine acceptable trade-offs of the potential complications related to those medications, and determine heterogeneity in preferences among patient subgroups.

Methods

A discrete choice experiment (DCE) was prospectively administered to orthopaedic trauma patients at a level-1 trauma center. DCEs are a quantitative technique used to measure individual preferences in a variety of health care settings by administering surveys that ask individuals to choose the best option between two or more hypothetical scenarios, or choice sets.[23-24,29] Options are described with a fixed set of attributes levels that vary in each scenario. The data collected

can be used to assess the relative importance of each attribute and acceptable trade-offs among attributes. An estimate of preference can be described as the marginal utility for a given attribute level. Marginal utility can be positive or negative, with numbers farther from zero indicating a stronger preference. Monetary costs can be included to produce willingness-to-pay estimates.

Study setting and population

This study was conducted at the R Adams Cowley Shock Trauma Center in Baltimore, Maryland and received prior approval by the Institutional Review Board at the University of Maryland School of Medicine. All adult (≥ 18 years) patients treated with pelvic or acetabular fractures or an operative extremity fracture were assessed for eligibility from November 2015 through February 2016. Patients who were unable to consent due to intubation or altered mental status and non-English speaking patients were excluded. Upon written consent, patients were enrolled in the study as inpatients or at an outpatient follow-up appointment within 4 months from their initial admission for their injury.

Study design

The attributes and their corresponding levels were selected based on a literature review, patient interviews, expert consultation, and a retrospective review of patient outcomes. Medication attributes used in the DCE included medication administration route (oral tablet vs. needle injection), cost, possible side effects including bruising or stomach pain, risk of having a bleeding complication that requires a blood transfusion, risk of having a wound complication that

requires another operation, risk of VTE requiring therapeutic anticoagulation for 6 months, and risk of death due to PE. These attributes were chosen to reflect medication qualities that patients are aware of when taking medications (route, cost, side effects) and clinically-important outcomes.

Forty choice sets were developed using a Bayesian D-optimal design with JMP Version 12 software (SAS Institute, Cary, NC) to ensure maximum variation in attribute comparison. The 40 choice sets were then randomly divided into four surveys, each with 10 choice sets, to minimize respondent burden. As documented by Sandor et al,[30] using heterogeneous designs produce substantial improvements in efficiency over a single survey and provides more precision in estimating true parameters. Each choice set compared two hypothetical VTE prophylaxis medications described by their attributes (**Figure 1**). 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. Demographic data including age, sex, race (as defined by the participant), type of injury, Injury Severity Score, American Society of Anesthesiologists (ASA) physical status, income, health insurance status, days on prophylaxis, and timing of recruitment (inpatient vs. outpatient) was collected from both the survey and the medical record. 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.

Data Analysis

Data collected through the DCE survey allows the quantification of and statistical inference about the relative importance of VTE prophylaxis medication attributes. A multinomial logit model,[32,33] with effects coding, was used to estimate patient preferences using marginal utility, willingness-to-pay (WTP), and acceptable trade-off estimates for a 1% reduction in VTE complications or side effects. Marginal utility is a measure of patient preference, with the estimate signifying the strength and direction of one's preference towards the attribute. With this analysis, we are able to determine the relative magnitude of patient preferences to avoid VTE-related complications in association with their medication choice. 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. All data analysis was conducted using the Choice Modeling platform in JMP Version 12.

Results

Of the 310 patients screened for participation, 50 were ineligible (40 unable to consent due to altered mental status, 8 non-English speaking, 2 contraindicated for VTE prophylaxis) and 28 (11%) patients refused participation. Of the 232 patients included in the analysis, the mean age was 47.9 years, with 56.9% male, and 66.8% were white. The majority of participants had a

lower extremity injury (83.6%), with a mean injury severity score of 11.7, and were fully insured (83.1%) (**Table 1**).

Patients most strongly preferred a reduction in risk of death by PE (marginal utility, 4.57; $P<0.0001$), distantly followed by a reduction in the risk of VTE requiring therapeutic anticoagulation, wound complications requiring another surgery, and bleeding complications requiring a transfusion (**Table 2**). Patients were willing to pay $1686.90 for a 1% absolute reduction in risk of death due to PE compared to $92.29 or less for a 1% absolute reduction in any of the other measured outcome variables. Patients also preferred to take oral tablets (marginal utility, 0.16; $P<0.0001$) and were willing to pay $117.45 to receive prophylaxis via oral route over subcutaneous injection. Possible medication side effects, such as stomach pain or bruising, did not significantly influence patient preferences ($P>0.1$).

To change patient preference in favor of injections requires a 6.98% absolute reduction in the risk of bleeding complications requiring transfusion, a 4.53% absolute reduction in the risk of wound complications requiring reoperation, and a 1.27% absolute reduction in risk of VTE requiring therapeutic anticoagulation (**Table 3**). In contrast, only a 0.07% absolute reduction in risk of death due to PE was needed to change patient preference.

In our subgroup analyses examining heterogeneity in preferences, patients who were female, white, or had lower extremity injuries demonstrated significantly stronger preference for oral VTE prophylaxis over subcutaneous injections ($P<0.05$) (**Table 4**). Patients with upper extremity injuries valued a reduction in risk of bleeding complications more than patients with lower extremity injuries ($P=0.01$). Patients who were recruited as an inpatient valued a reduction in risk of wound complications requiring reoperation more than patients who were recruited from the

outpatient clinic ($P<0.01$). There were no other significant associations between the tested covariates and our included VTE prophylaxis attributes.

Discussion

Consistent with previous studies,[22] our study demonstrates a strong patient preference for oral VTE prophylaxis over subcutaneous injection when all other relevant attributes are equal. However, patients only required a small reduction in the absolute risk of death due to PE to change their preference in favor of an injection. When choosing between VTE prophylaxis regimens, patients most valued (in order): risk of death due to PE, risk of VTE requiring therapeutic anticoagulation, risk of wound complications requiring reoperation, and risk of bleeding complications requiring transfusion. A defined reduction in any of these outcomes could change patient preference to favor the injection route. In addition, underlying patient factors such as sex, race, type of injury, and inpatient status led to significant heterogeneity in patient preferences.

To our knowledge, our study is the first to assess the weight of patient-valued outcomes regarding potential risks and complications of VTE prophylaxis. The study also determined patient characteristics associated with heterogeneity in their preferences. Previous studies have shown that patient refusal is a common reason for missed VTE doses and increases the risk of a VTE event.[19-22] Patient preference for oral medications is also well-documented.[22,25] Our study also demonstrates a strong preference for oral medications, but our results show that this preference can change if the risk of the aforementioned patient-important outcomes is high enough. Patients were particularly concerned about the risk of death due to PE, requiring only a

0.07% absolute reduction in risk of death to change patient preference in favor of an injection. In addition, only relatively small reductions in the risk of other outcomes were required to change patient preference. Furthermore, the preference for route varied significantly depending on the patient's sex, race, type of injury, and inpatient status.

While the design of the DCE enables the assessment of risk-benefit trade-offs among subgroups, it does not allow for qualitative analysis of patient preferences. 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. The greater value placed on risk of death due to PE compared to other outcome measures could be a result of death being the easiest outcome variable for the average patient to understand. We were unable to control for patient disposition in our analysis (home vs. rehab), but we did compare responses of inpatients to outpatients. Patients who were recruited as an inpatient were more concerned about the risk of reoperation than patients recruited as outpatients, potentially because their injury and initial operation were more recent in their memory. In addition, study participants had varying lengths of VTE prophylaxis prescribed at time of recruitment and some patients were closer to time of injury and initial operation than others. Although, when assessed, time since injury did not affect patient preferences.

Some participants had personal experience with one or more of the measured outcomes while others had no history of complications, which we were unable to control for in our final analysis. 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. Lastly, we did not collect data on patient education level which could affect the patient's understanding of certain outcomes, however income and insurance level may be surrogate markers for education and were included in the analysis.

In the current era of patient-centered healthcare, it is important that we consider all outcomes that patients value and the heterogeneity in those preferences when conducting clinical comparative effectiveness research and when making clinical guidelines in order to improve healthcare delivery and reduce cost.[26, 27,28] Our data demonstrate that orthopaedic trauma patients prefer VTE prophylaxis by oral tablet to prophylaxis by subcutaneous injection when all other relevant attributes are equal. However, the risk of death due to PE is the dominant concern when choosing a regimen. 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 trade-offs among subgroups in this important area of ongoing debate. In the era of patient-centered healthcare, future studies and clinical guideline recommendations comparing available VTE prophylaxis regimens should focus on the outcomes most important to patients and incorporate patient trade-off estimates to ensure their work is reflective of patient preferences.

Table 1 Characteristics of orthopaedic fracture participants (n=232)

Characteristic	Mean (SD)
Male, No. (%)	132 (56.9)
Age, y	47.9 (17.7)
Race, No. (%)	
White	155 (66.8)
Black	62 (26.7)
Other	8 (3.4)
Hispanic	7 (3.0)
Primary Orthopaedic Injury, No. (%)	
Lower Extremity	194 (83.6)
Upper Extremity	38 (16.4)
ASA,[1] No. (%)	
1	21 (9.1)
2	117 (50.4)
3	81 (34.9)
4	11 (4.7)
Unknown	2 (0.9)
Injury severity score (ISS)	11.7 (6.7)
Income, $USD, No. (%)	
<$10,000	46 (19.8)
$10,000 - $19,999	20 (8.6)
$20,000 - $34,999	35 (15.1)
$35,000-$49,999	24 (10.3)
$50,000 -$74,999	26 (11.1)
$75,000 - $100,000	24 (10.3)
>$100,000	35 (15.1)
Unknown	22 (9.5)
Health Insurance, No. (%)	
Fully Insured	193 (83.1)
Partially Insured	12 (5.2)
Uninsured	24 (10.3)
Unknown	3 (1.3)
Timing of recruitment No. (%)	
In-patient	78 (33.6)
Out-patient	154 (66.4)

Notes:

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

[2] 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).

Table 2 Patient preferences and valuation of venous thromboembolism prophylaxis attributes

Attribute	Level	Marginal Utility	95% CI	WTP	*P* Value
Route	Oral tablet	0.16	0.11 - 0.21	$117.45	<0.0001
	Injection	-0.16	-0.21 – -0.11	-	-
Side Effects	Bruising on leg	-0.04	-0.11 – 0.02	-$45.94	0.11
	Stomach pain	-0.04	-0.12 – 0.04	-$44.08	-
	No side effects	0.08	0.003 – 0.16	$45.08	-
Bleeding complications requiring transfusion	Reduce risk by 1%	0.05	0.04 – 0.05	$16.83	<0.0001
Wound complications requiring another surgery	Reduce risk by 1%	0.07	0.06 – 0.08	$25.91	<0.0001
Blood clot requiring long-term medication	Reduce risk by 1%	0.25	0.15 – 0.36	$92.29	<0.0001
Death due to PE	Reduce risk by 1%	4.57	3.26 – 5.89	$1686.90	<0.0001
Cost	$10 increase	-0.03	-0.04 – -0.02	Reference	<0.0001

PE = pulmonary embolism; CI = confidence interval; WTP = willingness to pay

Note: Marginal utility quantifies the additional satisfaction gained by the patient for each described attribute/level. Negative marginal utility values signify an aversion to or dissatisfaction with the described attribute/level. All risk reductions are absolute. 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 are based on the incremental change in level.

Table 3 The absolute risk reduction (ARR) of a potential complication that a patient would be willing to accept to change their route preference from oral to injection prophylaxis

Attribute	Acceptable ARR Trade-off
Bleeding complications requiring transfusion	6.98%
Wound complications requiring another surgery	4.53%
Blood clot requiring long-term medication	1.27%
Death due to PE	0.07%

ARR = absolute risk reduction; PE = pulmonary embolism

Table 4 Sub-group analysis quantifying heterogeneity in patient preferences

Attribute	Level	Sub-Group	Marginal Utility	95% CI	WTP	*P* Value
Route	Take oral tablet over injection	Sex [Female]	0.07	0.02 – 0.11	$201.24	<0.01
		Sex [Male]	-0.07	-0.11 - -0.02	$66.79	
		Race [White]	0.09	0.03 – 0.14	$182.23	<0.01
		Race [Black]	-0.09	-0.14 - -0.03	$18.48	
		Injury [Lower Extremity]	0.08	0.02 – 0.15	$132.38	0.01
		Injury [Upper Extremity]	-0.08	-0.15 - -0.02	$18.98	
Bleeding complications requiring transfusion	Reduce risk by 1%	Injury [Lower Extremity]	-0.02	-0.03 - -0.003	$14.50	0.01
		Injury [Upper Extremity]	0.02	0.003 – 0.03	$32.04	
Wound complications requiring another surgery	Reduce risk by 1%	Recruitment [In-patient]	0.02	0.003 – 0.03	$46.32	<0.01
		Recruitment [Out-patient]	-0.02	-0.03 – -0.003	$20.24	

CI = confidence interval; WTP = willingness to pay

Note: Marginal utility quantifies the additional satisfaction gained by the patient for each described attribute/level. Negative marginal utility values signify an aversion to or dissatisfaction with the described attribute/level. 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.

Figure 1: Sample question from the discrete choice experiment survey administered to participants. In each question the values for each hypothetical medication are varied.

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Author Contribution

BH contributed to the literature search, study design, data collection, data interpretation, writing, and critical revision. NNO contributed to the literature search, study design, data analysis, data interpretation, writing, and critical revision. CDMcontributed to the data interpretation and critical revision. DS, TTM, HJ, RVO, and GPS contributed to the literature search, study design, data interpretation, and critical revision. RC contributed to the study design, data analysis, data interpretation, and critical revision. All authors have approved the final version of the article submitted and agree to be accountable for all aspects of the work.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years other than those listed below; no other relationships or activities that could appear to have influenced the submitted work apart from the following:

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Data sharing statement

No additional data are available.

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Which medication would you prefer?

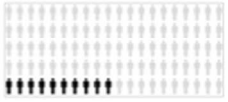
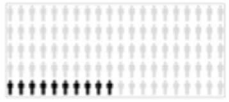
	Medication A		Medication B
Type of daily medication	Oral pill		Needle injection
What will it **cost** you	$100		$50
Possible **side effect**	None		Bruising on leg
Chance that you will have a bleeding complication and need a **blood transfusion**	10 out of 1000		100 out of 1000 
Chance that you will have wound complication and need **another operation**	50 out of 1000 		100 out of 1000 
Chance that you will have a blood clot and have to take **medications for 6 months**	20 out of 1000 		10 out of 1000
Chance of **death** due to a pulmonary embolism	1 out of 1000		1 out of 1000
Check one	Prefer **Medication A** ☐		Prefer **Medication B** ☐

Figure 1. Sample question from the discrete choice experiment survey administered to participants. In each question the values for each hypothetical medication are varied.

172x209mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page 1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Page 4-5**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page 5**
Methods		
Study design	4	Present key elements of study design early in the paper **Page 5-6**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 6**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants **Page 6**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page 6-7**
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 **Page 7**
Bias	9	Describe any efforts to address potential sources of bias **Page 7-8**
Study size	10	Explain how the study size was arrived at **Page 7**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **Page 7-8**
		(*b*) Describe any methods used to examine subgroups and interactions **Page 7-8**
		(*c*) Explain how missing data were addressed **Page 7-8**
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses **Page 7-8**
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 **Page 8**
		(b) Give reasons for non-participation at each stage **Page 8**
		(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 **Page 8**
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures **Page 8**
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 **Page 9**
		(*b*) Report category boundaries when continuous variables were categorized **Page 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 **Page 9**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Page 9**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page 10-11**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Page 11**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Page 10**
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 **Page 17**

*Give information separately for exposed and unexposed groups.

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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Patient Preferences for Venous Thromboembolism Prophylaxis After Injury: A Discrete Choice Experiment

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Patient Preferences for Venous Thromboembolism Prophylaxis After Injury: A Discrete Choice Experiment

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Abstract

Objective: Limited evidence for the optimal venous thromboembolism (VTE) prophylaxis regimen in orthopaedic trauma leads to variability in regimens. We sought to delineate patient preferences towards cost, complication profile, and administration route (oral tablet vs. subcutaneous injection).

Design: Discrete choice experiment (DCE).

Setting: Level 1 trauma center in Baltimore, USA.

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

Primary and secondary outcome measures: Relative preferences and trade-off estimates for a 1% reduction in complications were estimated using multinomial logit modelling. Interaction terms were added to the model to assess heterogeneity in preferences.

Results: Patients preferred oral tablets over subcutaneous injections (marginal utility, 0.16; 95% CI: 0.11 - 0.21, $P<0.0001$). Preferences changed in favor of subcutaneous injections with an absolute risk reduction of 6.98% in bleeding, 4.53% in wound complications requiring reoperation, 1.27% in VTE, and 0.07% in death from pulmonary embolism (PE). Patient characteristics (sex, race, type of injury, time since injury) affected patient preferences ($P<0.01$).

Conclusions: Patients preferred oral prophylaxis and were most concerned about risk of death from PE. Furthermore, the findings estimated the trade-offs acceptable to patients and heterogeneity in preferences for VTE prophylaxis.

Strengths and limitations of this study:

- This study quantifies patient preferences for venous thromboembolism prophylaxis in a high risk, and often difficult to research, population.
- The results provide valuable benefit-risk tradeoffs estimates to guide clinicians in a common decisional dilemma.
- High face validity in the choice sets is demonstrated by the directionality, magnitude, and consistency of the responses.
- The high response rate captured in this prospective study reduces response bias present in other survey methods.
- The choice sets presented to respondents were hypothetical scenarios, and the respondent's actual choices may be different.

Manuscript Text (Word Count: 2349)

Introduction

Traumatic injury is a well-described risk factor for the development of venous thromboembolism (VTE). The incidence of VTE among trauma patients ranges from 20 to 90% without any preventative measure.[1] In addition, pulmonary embolism (PE) is the third most common cause of death in patients who survive the first 24 hours following injury.[1-4] Orthopaedic trauma patients in particular have several well-known risk factors for VTE placing them at exceptionally high risk.[2, 5-8] Fortunately, chemoprophylaxis has been shown to significantly reduce the incidence of VTE in this population.[9] However controversy exists as to the optimal VTE prophylaxis regimen in orthopaedic trauma patients.[10-15]

For many orthopaedic populations, the American College of Chest Physicians (CHEST) and the Eastern Association for the Surgery of Trauma recommend enoxaparin (low molecular weight heparin (LMWH)) by subcutaneous injection for VTE prophylaxis, but recent studies show that acetylsalicylic acid (aspirin), an oral tablet, may be an equally effective alternative with lower risk of bleeding complications.[10-15] However, only limited data is available specific to orthopaedic trauma patients who may have even higher risk for both VTE events and bleeding.[16] The Orthopaedic Trauma Association Evidence Based Quality Value and Safety Committee highlights variability in prescribed regimens due to the poor scientific support for various regimens and emphasizes the need for guidelines to improve patient care.[17]

The CHEST guidelines emphasize the need for systematic reviews of patient values and preferences when creating guidelines for specific populations.[18] Creation of guidelines requires making risk and benefit trade-offs, and patient values regarding VTE prophylaxis depend on the

health outcomes considered. Furthermore, defining the heterogeneity of preferences in this patient population is necessary to provide valuable individualized VTE prevention options. Implementing guidelines that consider patient preferences may increase patient satisfaction with and improve adherence to clinical treatments.[19] Patient medication refusal is a leading cause of non-administration of VTE prophylaxis in inpatients, and missed doses are highly associated with increased VTE incidence.[20-22] In a study of medical and surgical patient preferences for VTE prophylaxis regimens, the majority of patients preferred oral administration over subcutaneous injection if all other factors were equal.[23] Patients who preferred subcutaneous administration presumed a faster onset of action and were less likely to refuse administration.

Existing VTE prevention studies do not evaluate patient preferences, investigate acceptable trade-offs of the risks and benefits of those medications, or determine heterogeneity in preferences based on demographic and clinical characteristics. The purpose of this study was to elicit the preferences of orthopaedic trauma patients towards currently available VTE prophylaxis, examine acceptable trade-offs of the potential complications related to those medications, and determine heterogeneity in preferences among patient subgroups.

Methods

A discrete choice experiment (DCE) was prospectively administered to orthopaedic trauma patients at a level-1 trauma center. DCEs are a quantitative technique used to measure individual preferences in a variety of health care settings by administering surveys that ask individuals to choose the best option between two or more hypothetical scenarios, or choice sets.[24-26] Options are described with a fixed set of attributes levels that vary in each scenario. The data collected

can be used to assess the relative importance of each attribute and acceptable trade-offs among attributes. An estimate of preference can be described as the marginal utility for a given attribute level. Marginal utility can be positive or negative, with numbers farther from zero indicating a stronger preference. Monetary costs can be included to produce willingness-to-pay estimates.

Study setting and population

This study was conducted at the R Adams Cowley Shock Trauma Center in Baltimore, Maryland and received prior approval by the Institutional Review Board at the University of Maryland School of Medicine. All adult (≥ 18 years) patients treated with pelvic or acetabular fractures or an operative extremity fracture were assessed for eligibility from November 2015 through February 2016. Patients who were unable to consent due to intubation or altered mental status and non-English speaking patients were excluded. Upon written consent, patients were enrolled in the study as inpatients or at an outpatient follow-up appointment within 4 months from their initial admission for their injury.

Study design

The attributes and their corresponding levels were selected based on a literature review, patient interviews, expert consultation, and a retrospective review of patient outcomes. Medication attributes used in the DCE included medication administration route (oral tablet vs. subcutaneous injection), cost, possible side effects including bruising or stomach pain, risk of having a bleeding complication that requires a blood transfusion, risk of having a wound complication that

requires another operation, risk of VTE requiring therapeutic anticoagulation for 6 months, and risk of death due to PE. These attributes were chosen to reflect medication qualities that patients are aware of when taking medications (route, cost, side effects) and clinically-important outcomes. 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.

Forty choice sets were developed using a Bayesian D-optimal design with JMP Version 12 software (SAS Institute, Cary, NC) to ensure maximum variation in attribute comparison. The 40 choice sets were then randomly divided into four surveys, each with 10 choice sets, to minimize respondent burden. As documented by Sandor et al,[27] using heterogeneous designs produce substantial improvements in efficiency over a single survey and provides more precision in estimating true parameters. Each choice set compared two hypothetical VTE prophylaxis medications described by their attributes (**Figure 1**). 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. Demographic data including age, sex, race (as defined by the participant), type of injury, Injury Severity Score, American Society of Anesthesiologists (ASA) physical status, income, health insurance status, days on prophylaxis, and timing of recruitment (inpatient vs. outpatient) was collected from both the survey and the medical record. 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.

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.[28] Based on this calculation,[28] 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.

Data Analysis

Data collected through the DCE survey allows the quantification of and statistical inference about the relative importance of VTE prophylaxis medication attributes. A multinomial logit model,[29,30] with effects coding, was used to estimate patient preferences using marginal utility, willingness-to-pay (WTP), and acceptable trade-off estimates for a 1% reduction in VTE complications or side effects. Marginal utility is a measure of patient preference, with the estimate signifying the strength and direction of one's preference towards the attribute. With this analysis, we are able to determine the relative magnitude of patient preferences to avoid VTE-related complications in association with their medication choice. 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. All data analysis was conducted using the Choice Modeling platform in JMP Version 12.

Results

Of the 310 patients screened for participation, 50 were ineligible (40 unable to consent due to altered mental status, 8 non-English speaking, 2 contraindicated for VTE prophylaxis) and 28 (11%) patients refused participation. Of the 232 patients included in the analysis, the mean age was 47.9 years, with 56.9% male, and 66.8% were white. The majority of participants had a lower extremity injury (83.6%), with a mean injury severity score of 11.7, and were fully insured (83.1%) (**Table 1**).

Patients most strongly preferred a reduction in risk of death by PE (marginal utility, 4.57; $P<0.0001$), distantly followed by a reduction in the risk of VTE requiring therapeutic anticoagulation, wound complications requiring another surgery, and bleeding complications requiring a transfusion (**Table 2**). Patients were willing to pay $1686.90 for a 1% absolute reduction in risk of death due to PE compared to $92.29 or less for a 1% absolute reduction in any of the other measured outcome variables. Patients also preferred to take oral tablets (marginal utility, 0.16; $P<0.0001$) and were willing to pay $117.45 to receive prophylaxis via oral route over subcutaneous injection. Possible medication side effects, such as stomach pain or bruising, did not significantly influence patient preferences ($P>0.1$).

To change patient preference in favor of subcutaneous injections requires a 6.98% absolute reduction in the risk of bleeding complications requiring transfusion, a 4.53% absolute reduction

in the risk of wound complications requiring reoperation, and a 1.27% absolute reduction in risk of VTE requiring therapeutic anticoagulation (**Table 3**). In contrast, only a 0.07% absolute reduction in risk of death due to PE was needed to change patient preference.

In our subgroup analyses examining heterogeneity in preferences, patients who were female, white, or had lower extremity injuries demonstrated significantly stronger preference for oral VTE prophylaxis over subcutaneous injections ($P<0.05$) (**Table 4**). Patients with upper extremity injuries valued a reduction in risk of bleeding complications more than patients with lower extremity injuries ($P=0.01$). Patients who were recruited as an inpatient valued a reduction in risk of wound complications requiring reoperation more than patients who were recruited from the outpatient clinic ($P<0.01$). There were no other significant associations between the tested covariates and our included VTE prophylaxis attributes.

Discussion

Consistent with previous studies,[23] our study demonstrates a strong patient preference for oral VTE prophylaxis over subcutaneous injection when all other relevant attributes are equal. However, patients only required a small reduction in the absolute risk of death due to PE to change their preference in favor of a subcutaneous injection. When choosing between VTE prophylaxis regimens, patients most valued (in order): risk of death due to PE, risk of VTE requiring therapeutic anticoagulation, risk of wound complications requiring reoperation, and risk of bleeding complications requiring transfusion. A defined reduction in any of these outcomes could change patient preference to favor the subcutaneous injection route. In addition,

underlying patient factors such as sex, race, type of injury, and inpatient status led to significant heterogeneity in patient preferences.

To our knowledge, our study is the first to assess the weight of patient-valued outcomes regarding potential risks and complications of VTE prophylaxis. The study also determined patient characteristics associated with heterogeneity in their preferences. Previous studies have shown that patient refusal is a common reason for missed VTE doses and increases the risk of a VTE event.[20-23] Patient preference for oral medications is also well-documented.[23,31] Our study also demonstrates a strong preference for oral medications, but our results show that this preference can change if the risk of the aforementioned patient-important outcomes is high enough. Patients were particularly concerned about the risk of death due to PE, requiring only a 0.07% absolute reduction in risk of death to change patient preference in favor of a subcutaneous injection. In addition, only relatively small reductions in the risk of other outcomes were required to change patient preference. Furthermore, the preference for route varied significantly depending on the patient's sex, race, type of injury, and inpatient status.

While the design of the DCE enables the assessment of risk-benefit trade-offs among subgroups, it does not allow for qualitative analysis of patient preferences. 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. The greater value placed on risk of death due to PE compared to other outcome measures could be a result of death being the easiest outcome variable for the average patient to understand. We were unable to control for patient disposition in our analysis (home vs. rehab), but we did compare responses of inpatients to outpatients. Patients who were recruited as an inpatient were more concerned about the risk of reoperation than patients recruited as outpatients, potentially because their injury and

initial operation were more recent in their memory. In addition, study participants had varying lengths of VTE prophylaxis prescribed at time of recruitment and some patients were closer to time of injury and initial operation than others. Although, when assessed, time since injury did not affect patient preferences.

Some participants had personal experience with one or more of the measured outcomes while others had no history of complications, which we were unable to control for in our final analysis. 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. Lastly, we did not collect data on patient education level which could affect the patient's understanding of certain outcomes, however income and insurance level may be surrogate markers for education and were included in the analysis.

In the current era of patient-centered healthcare, it is important that we consider all outcomes that patients value and the heterogeneity in those preferences when conducting clinical comparative effectiveness research and when making clinical guidelines in order to improve healthcare delivery and reduce cost.[19,32,33] Our data demonstrate that orthopaedic trauma patients prefer VTE prophylaxis by oral tablet to prophylaxis by subcutaneous injection when all other relevant attributes are equal. However, the risk of death due to PE is the dominant concern when choosing a regimen. 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 trade-offs among subgroups in this important area of ongoing debate. In the era of patient-centered

healthcare, future studies and clinical guideline recommendations comparing available VTE prophylaxis regimens should focus on the outcomes most important to patients and incorporate patient trade-off estimates to ensure their work is reflective of patient preferences.

Table 1 Characteristics of orthopaedic fracture participants (n=232)

Characteristic	Mean (SD)
Male, No. (%)	132 (56.9)
Age, y	47.9 (17.7)
Race, No. (%)	
White	155 (66.8)
Black	62 (26.7)
Other	8 (3.4)
Hispanic	7 (3.0)
Primary Orthopaedic Injury, No. (%)	
Lower Extremity	194 (83.6)
Upper Extremity	38 (16.4)
ASA,[1] No. (%)	
1	21 (9.1)
2	117 (50.4)
3	81 (34.9)
4	11 (4.7)
Unknown	2 (0.9)
Injury severity score (ISS)	11.7 (6.7)
Income, $USD, No. (%)	
<$10,000	46 (19.8)
$10,000 - $19,999	20 (8.6)
$20,000 - $34,999	35 (15.1)
$35,000-$49,999	24 (10.3)
$50,000 -$74,999	26 (11.1)
$75,000 - $100,000	24 (10.3)
>$100,000	35 (15.1)
Unknown	22 (9.5)
Health Insurance, No. (%)	
Fully Insured	193 (83.1)
Partially Insured	12 (5.2)
Uninsured	24 (10.3)
Unknown	3 (1.3)
Timing of recruitment No. (%)	
In-patient	78 (33.6)
Out-patient	154 (66.4)

Notes:

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

[2] 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).

Table 2 Patient preferences and valuation of venous thromboembolism prophylaxis attributes

Attribute	Level	Marginal Utility	95% CI	WTP	*P* Value
Route	Oral tablet	0.16	0.11 - 0.21	$117.45	<0.0001
	Subcutaneous injection	-0.16	-0.21 – -0.11	-	-
Side Effects	Bruising on leg	-0.04	-0.11 – 0.02	-$45.94	0.11
	Stomach pain	-0.04	-0.12 – 0.04	-$44.08	-
	No side effects	0.08	0.003 – 0.16	$45.08	-
Bleeding complications requiring transfusion	Reduce risk by 1%	0.05	0.04 – 0.05	$16.83	<0.0001
Wound complications requiring another surgery	Reduce risk by 1%	0.07	0.06 – 0.08	$25.91	<0.0001
Blood clot requiring long-term medication	Reduce risk by 1%	0.25	0.15 – 0.36	$92.29	<0.0001
Death due to PE	Reduce risk by 1%	4.57	3.26 – 5.89	$1686.90	<0.0001
Cost	$10 increase	-0.03	-0.04 – -0.02	Reference	<0.0001

PE = pulmonary embolism; CI = confidence interval; WTP = willingness to pay

Note: Marginal utility quantifies the additional satisfaction gained by the patient for each described attribute/level. Negative marginal utility values signify an aversion to or dissatisfaction with the described attribute/level. All risk reductions are absolute. 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 are based on the incremental change in level.

Table 3 The absolute risk reduction (ARR) of a potential complication that a patient would be willing to accept to change their route preference from oral to subcutaneous injection prophylaxis

Attribute	Acceptable ARR Trade-off
Bleeding complications requiring transfusion	6.98%
Wound complications requiring another surgery	4.53%
Blood clot requiring long-term medication	1.27%
Death due to PE	0.07%

ARR = absolute risk reduction; PE = pulmonary embolism

Table 4 Sub-group analysis quantifying heterogeneity in patient preferences

Attribute	Level	Sub-Group	Marginal Utility	95% CI	WTP	*P* Value
Route	Take oral tablet over subcutaneous injection	Sex [Female]	0.07	0.02 – 0.11	$201.24	<0.01
		Sex [Male]	-0.07	-0.11 - -0.02	$66.79	
		Race [White]	0.09	0.03 – 0.14	$182.23	<0.01
		Race [Black]	-0.09	-0.14 - -0.03	$18.48	
		Injury [Lower Extremity]	0.08	0.02 – 0.15	$132.38	0.01
		Injury [Upper Extremity]	-0.08	-0.15 - -0.02	$18.98	
Bleeding complications requiring transfusion	Reduce risk by 1%	Injury [Lower Extremity]	-0.02	-0.03 - -0.003	$14.50	0.01
		Injury [Upper Extremity]	0.02	0.003 – 0.03	$32.04	
Wound complications requiring another surgery	Reduce risk by 1%	Recruitment [In-patient]	0.02	0.003 – 0.03	$46.32	<0.01
		Recruitment [Out-patient]	-0.02	-0.03 – -0.003	$20.24	

CI = confidence interval; WTP = willingness to pay

Note: Marginal utility quantifies the additional satisfaction gained by the patient for each described attribute/level. Negative marginal utility values signify an aversion to or dissatisfaction with the described attribute/level. 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 a subcutaneous injection. However, females are willing to pay more for an oral tablet over a subcutaneous injection than males are willing to pay for that same tradeoff (oral tablet over subcutaneous injection). Willingness to pay values for attributes with continuous levels estimate the willingness to pay for an additional 1% absolute reduction in risk.

Figure 1: Sample question from the discrete choice experiment survey administered to participants. In each question the values for each hypothetical medication are varied.

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Author Contribution

BH contributed to the literature search, study design, data collection, data interpretation, writing, and critical revision. NNO contributed to the literature search, study design, data analysis, data interpretation, writing, and critical revision. CDMcontributed to the data interpretation and critical revision. DS, TTM, HJ, RVO, and GPS contributed to the literature search, study design, data interpretation, and critical revision. RC contributed to the study design, data analysis, data interpretation, and critical revision. All authors have approved the final version of the article submitted and agree to be accountable for all aspects of the work.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years other than those listed below; no other relationships or activities that could appear to have influenced the submitted work apart from the following:

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Data sharing statement

No additional data are available.

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Which medication would you prefer?

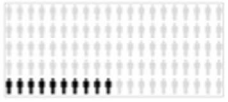
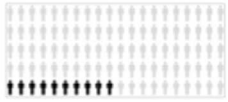
	Medication A		Medication B
Type of daily medication	Oral pill		Needle injection
What will it **cost** you	$100		$50
Possible **side effect**	None		Bruising on leg
Chance that you will have a bleeding complication and need a **blood transfusion**	10 out of 1000		100 out of 1000 
Chance that you will have wound complication and need **another operation**	50 out of 1000 		100 out of 1000 
Chance that you will have a blood clot and have to take **medications for 6 months**	20 out of 1000 		10 out of 1000
Chance of **death** due to a pulmonary embolism	1 out of 1000		1 out of 1000
Check one	Prefer **Medication A** ☐		Prefer **Medication B** ☐

Figure 1. Sample question from the discrete choice experiment survey administered to participants. In each question the values for each hypothetical medication are varied.

172x209mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Page 1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Page 2**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Page 4-5**
Objectives	3	State specific objectives, including any prespecified hypotheses **Page 5**
Methods		
Study design	4	Present key elements of study design early in the paper **Page 5-6**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Page 6**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants **Page 6**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Page 6-7**
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 **Page 7**
Bias	9	Describe any efforts to address potential sources of bias **Page 7-8**
Study size	10	Explain how the study size was arrived at **Page 7**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **Page 7-8**
		(*b*) Describe any methods used to examine subgroups and interactions **Page 7-8**
		(*c*) Explain how missing data were addressed **Page 7-8**
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses **Page 7-8**
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 **Page 8**
		(b) Give reasons for non-participation at each stage **Page 8**
		(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 **Page 8**
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures **Page 8**
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 **Page 9**
		(*b*) Report category boundaries when continuous variables were categorized **Page 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 **Page 9**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Page 9**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Page 10-11**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Page 11**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Page 10**
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 **Page 17**

*Give information separately for exposed and unexposed groups.

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.