

# Physicians' perceptions of the definition of major bleeding in major orthopedic surgery: results of an international survey

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**Abstract** Decisions regarding choice of thromboprophylaxis in patients undergoing major orthopedic surgery are based on assessment of individual patient risk for thrombosis versus risk for bleeding. An international survey sought physician views on definitions and relative importance of different types of major bleeding. A random sample of physicians from five countries (100 physicians per country, mainly surgeons) completed an internet-based 13-question survey on perceptions, concerns, and relevance of bleeding associated with thromboprophylaxis in major orthopedic surgery. Over 80% of responders were concerned or very concerned about bleeding with >70% considering surgical-site bleeding as the most concerning, and relevant type and site for bleeding. Nearly 80% of responders considered surgical-site bleeding to increase patient length of hospital stay, and >70% noted that it complicates patient rehabilitation. After fatal bleeding, bleeding leading to re-operation was ranked as the most concerning type of major bleed. Less than half of responders reported closely reading the major-bleeding definitions in clinical study publications. Most responders favored anticoagulants that could offer a reduced bleeding risk and similar venous thromboembolism (VTE) prevention compared to current anticoagulants rather than a decrease in VTE and similar bleeding risk. There is a disconnect between the definitions of major bleeding that surgeons would apply to describe bleeding associated with

VTE thromboprophylaxis, and those used in clinical studies reporting the safety profiles of newer anticoagulant agents. Misperceptions about the benefit-to-harm profiles of thromboprophylactic therapies may incorrectly inform treatment choices in patients at high risk for post-operative VTE.

**Keywords** Major bleeding · Orthopedic surgery · Survey · Thromboprophylaxis

## Introduction

There are multiple prophylactic agents available for the prevention of venous thromboembolism (VTE) after major orthopedic surgery [1]. Current international, evidence-based guidelines, such as those issued by the American College of Chest Physicians, specifically recommend the use of unfractionated heparin, low-molecular-weight heparin (LMWH), and fondaparinux for the prevention of VTE after major orthopedic surgery [1]. Newer agents, such as rivaroxaban [2–5], dabigatran [6–8], and apixaban [9], which have an oral route of administration, are being developed for use as thromboprophylaxis in major orthopedic surgery patients.

Each of the available thromboprophylactic agents has advantages and disadvantages, and evaluation of the benefit versus risk profile of any chosen drug therapy is crucial [10]. The decision to provide thromboprophylaxis and the choice of agent selected, is often based on an assessment of an individual patient's risk for thrombosis versus their risk for bleeding complications. Monitoring and quantification of bleeding associated with a given therapy is particularly important as this will have an impact on the: treatment and regimen the patient will receive; likelihood of the patient

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requiring pre- or post-operative transfusion; and pre-operative strategy developed between the surgeon and anesthesiologist (such as use of erythropoietin, and any plans for self-transfusion or blood salvage in the peri-operative and post-operative periods).

In randomized clinical trials, new anticoagulant and antithrombotic agents are typically assessed in terms of their efficacy relative to established LMWH prophylaxis—although safety endpoint definitions applied in such studies can vary [11]. Bleeding definitions used in clinical trial programs for the development of new agents can differ substantially, and in particular with regard to whether major bleeding does or does not include surgical-site bleeding [11, 12].

We report the findings of an international survey of orthopedic surgeons designed to determine the surgeon views on the relative importance of factors (e.g. type of bleeding, site of bleeding, bleeding rates, and efficacy and adverse event profiles of thromboprophylactic agents) affecting their choice of prophylaxis for major orthopedic surgery patients. The survey also sought information on the key concerns of practicing orthopedic surgeons regarding thromboprophylaxis and their relevance to endpoints used in clinical trials.

## Methods

### Survey participants

The study was an international, online survey of practicing orthopedic surgeons from Germany, Spain, France, and the UK and USA. In France, anesthesiologists were also invited to participate in the survey because both anesthesiologists and orthopedic surgeons prescribe and administer VTE prophylaxis to hospitalized patients. Recruitment of physician participants was achieved by email invitations to a random sample per country. In some cases, reminder emails were used to aid recruitment. To avoid potential sampling bias, the subject of the survey was not included in the invitation email title.

Once a physician had responded to the invitation to participate, they received a unique code to access the online survey questions. Potential participants were then asked to complete a screening questionnaire to establish their eligibility for taking part in the survey. In order to be eligible, physicians had to declare no relationship or affiliation with advertising, pharmaceutical company, market research, or biotechnology companies; they had to have between 5 and 29 years of professional experience and had to be involved in the initiation of VTE prophylaxis, and to perform (or provide the anesthesia for) more than five major orthopedic surgical procedures (total hip replacement [THR] or total

knee arthroplasty [TKA]) in a typical working month. For their views to be included in the survey evaluation, physicians were required to meet these inclusion criteria and to complete the online survey before the database was closed. To avoid any potential bias resulting from the exclusion of any completed surveys received, the number of survey participants was stopped when 100 surveys were received. All responders to the email invitation received an incentive to complete the survey.

### Survey design

The survey design had been previously tested in all participating countries. The final survey comprised 13 questions (some with sub-questions) that took participants approximately 20 min to complete. The focus of the survey questions was on perceptions, concerns, and relevance of bleeding associated with thromboprophylaxis in major orthopedic surgery. The 13 questions incorporated in the survey are listed in Table 1. All survey questions were translated into the respective languages of the included countries.

The survey included open-ended questions requiring spontaneous answers, together with closed-ended questions regarding bleeding risk where possible answers were to be based on a 4-point Likert scale and could range from: 1 = “very concerned/highly relevant”, 2 = “concerned/relevant”, 3 = “slightly concerned/relevant”, and 4 = “not concerned/relevant at all”; or 1 = “very likely” through to 4 = “don’t know”.

To assess the physician-perceived relevance of the bleeding endpoints for inclusion in the definition for major bleeding, the survey responders were asked to rank the five bleeding criteria (fatal bleeding; bleeding leading to re-operation; bleeding involving a critical organ; bleeding requiring a certain number of transfusions of red blood cells; bleeding leading to a certain drop in hemoglobin levels) from 1 to 5, where 1 was most important and 5 least important. All answers ranked position “1” were interpreted as being highly relevant for inclusion.

### Statistical analyses

Final survey results for each participating country were compared with the overall average figures using Student’s *t*-test. The threshold for significance was set at  $P = 0.05$ . Statistical analyses were performed using SPSS Statistics software version 17.0 (Paris, France).

## Results

In total, 5303 physicians from across Germany, Spain, France, and the USA and UK were invited to participate in

**Table 1** Key questions included in the survey

Survey questions	
Q1	While operating (THR or TKA), how concerned are you about bleeding?
Q2	What types of bleeding concern you the most in your patients undergoing THR or TKA?
Q3	Which are the bleeding sites that concern you most?
Q4	What is your level of concern about surgical-site bleeding?
Q5	Rank the following endpoints in importance: increase in major bleeding; increase in surgical-site bleeding; increase in overt bleeding; increase in clinically relevant non-major bleeding; increase in minor bleeding.
Q6	Please indicate the relevance of the following items in a definition of major bleeding that includes hematoma: fatal bleeding; bleeding leading to re-operation; bleeding affecting a critical organ; bleeding requiring a certain level of RBC transfusions; bleeding leading to a certain degree drop in Hb.
Q7	Would an increase in surgical-site bleeding (including hematoma) be at least as important as an increase in extra-surgical-site bleeding?
Q8	What is the relevance of the following items for defining surgical-site bleeding: level of transfusion needed; drop in Hb.
Q9	Do you usually read detailed definitions of bleeding types in journal articles?
Q10	Do you think journal articles provide bleeding definitions in a sufficiently clear way to readers?
Q11	How likely is it that experiencing an increase in surgical-site bleeding will impact on: patient length of stay (increasing duration); post-operative physiotherapy (delays/difficulties).
Q12	Indicate how likely the following outcomes are to affect your choice of anticoagulant: bleeding leading to increased in-patient stay; bleeding leading to delay/difficulties in physiotherapy.
Q13	If you had to choose between these two agents, which would you use for VTE prophylaxis: drug A (reduced bleeding rate compared with current anticoagulants and same level of VTE prevention) or drug B (better VTE prevention compared with current anticoagulants with the same bleeding rate).

THR total hip replacement, TKA total knee arthroplasty, RBC red blood cells, Hb hemoglobin

the survey and of these 789 responded to the invitation. Responder rates varied from 12% to 19% across the five participating countries. The number of survey participants was stopped when 100 surveys were received; therefore, completed surveys were obtained from 100 physicians from each country. In France, this number comprised 50 surveys completed by orthopedic surgeons and 50 surveys completed by anesthesiologists.

Demographic and professional/work-setting details of the physicians who completed this survey are shown in Table 2.

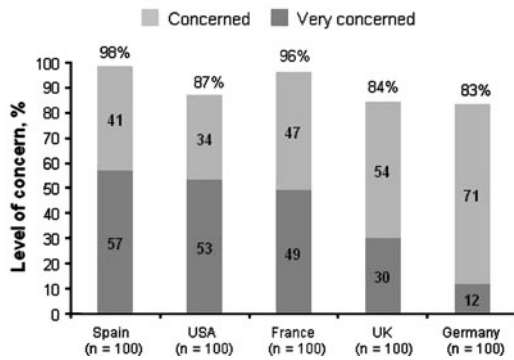
#### Levels of concern regarding bleeding

Over 80% of responders, across all participating countries, reported being “concerned” or “very concerned” about bleeding while performing THR or TKA operations. The country-specific responses ranged from 83% in Germany, to 96 and 98% in France and in Spain, respectively (Fig. 1). The proportion of responders who reported being “very concerned” about bleeding events while operating varied substantially between participating countries, ranging from 12% in Germany to 57% in Spain (Fig. 1).

**Table 2** Survey participants

	Germany	Spain	France		UK	USA
	Orthopedic	Orthopedic	Orthopedic	Anesthesiologists	Orthopedic	Orthopedic
Invited to participate ( <i>n</i> )	885	1210	598	790	990	830
Total responders ( <i>n</i> )	167	150	70	108	150	144
Total completed surveys	100	100	50	50	100	100
Survey participant characteristics						
Male (%)	90	90	98	80	98	98
Primarily worked in hospital (%)	80	80	88	98	100	20
Primarily worked in office (%)	20	20	12	2	0	80

Q1. While operating (THR or TKA), how concerned are you about bleeding?



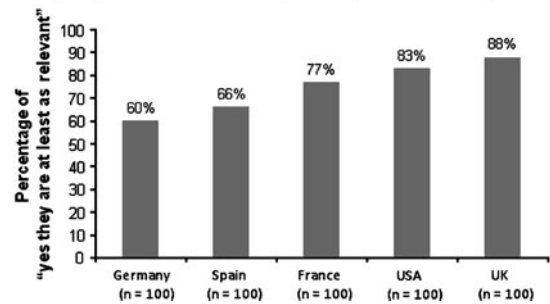
**Fig. 1** Levels of concern/relevance about bleeding while physicians are performing total hip replacement (THR) or total knee arthroplasty (TKA) surgery

Comparative importance of different bleeding events according to type and site

Physicians were asked what types of bleeding concerned them the most in patients undergoing major orthopedic surgery. Types of bleeding of concern included the broad categories of surgical-site, post-operative, and extra-surgical-site bleeding, as well as the degree (or extent of bleeding) and other forms of bleeding. Surgical-site bleeding was the bleeding event of most concern for half of all responders in the USA, and up to 71% of responders in France and the UK. Only 2–11% of responders across all countries considered extra-surgical-site bleeding as the bleeding event that concerned them the most. When a related question was asked about the bleeding site that causes most concern in patients undergoing major orthopedic surgery, up to 96% of responders reported that bleeding at the site of surgery was of most concern (Table 3).

Physician concern over surgical-site bleeding was also noted in response to a question asking about the relative importance of an increase in surgical-site bleeding, including hematoma, relative to an increase in extra-

Q7. Would an increase in surgical-site bleeding (including hematoma) be at least as important as an increase in extra-surgical-site bleeding?



**Fig. 2** Importance of surgical-site bleeding versus extra-surgical-site bleeding to physicians

surgical-site bleeding. The proportion of responders who considered increased surgical-site bleeding to be at least as important as extra-surgical-site bleeding varied from 60% in Germany to 88% in the UK (Fig. 2).

Impact of increased surgical-site bleeding

The perceived practical impact of surgical-site bleeding, in terms of its potential to increase the duration of post-operative hospital stay or to cause delays or difficulties in physiotherapy, is shown in Fig. 3. Up to 79% of responders considered an increase in surgical-site bleeding as very likely to be associated with a longer hospital stay. Up to 71% felt surgical-site bleeding could delay or complicate post-operative rehabilitation. Responses in Germany were slightly different from those in other countries. In Germany there appears to be a perception that surgical-site bleeding is less likely to have a negative impact on length of stay or physiotherapy.

Bleeding events considered appropriate for inclusion in a definition of major bleeding

Physicians were questioned on the relevance of different items that are often included within the definition of

**Table 3** The sites of bleeding that cause the most concern or are the most relevant for physicians undertaking major orthopedic surgery

Bleeding sites (%)	Spain (n = 100)	USA (n = 100)	France (n = 100)	UK (n = 100)	Germany (n = 100)	Overall (N = 500)
Surgical-site bleeding	60*	96 <sup>†</sup>	90	90	84	84
Post-operative bleeding	14 <sup>†</sup>	2	4	2	6	6
Extra-surgical-site bleeding	12 <sup>†</sup>	1*	9	5	1*	9
Degree of bleeding	7 <sup>†</sup>	1	0	6	1	3
“Other” bleeding events	15 <sup>†</sup>	7	3*	6	11	8

\* Level of concern in a specific country is significantly lower ( $P < 0.05$ ) compared with level observed in overall countries average

<sup>†</sup> Level of concern in a specific country is significantly higher ( $P < 0.05$ ) compared with level observed in overall countries average

Q11. How likely is it that experiencing an increase in surgical-site bleeding will impact on:

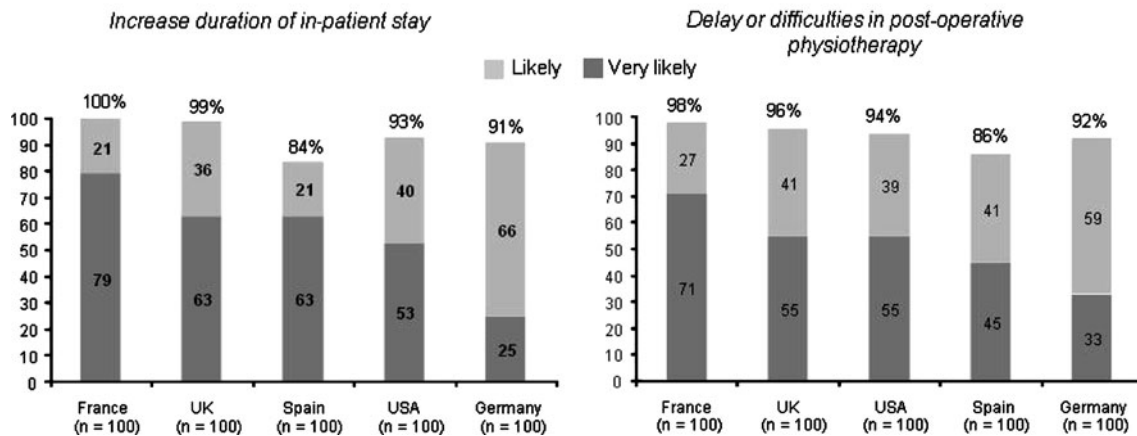


Fig. 3 Perceived impact of surgical-site bleeding on hospital stay and physiotherapy

“major bleeding” in clinical study reports and publications about anticoagulant VTE thromboprophylaxis. The major bleeding events that physicians were asked to rank included fatal bleeding, bleeding leading to re-operation, bleeding affecting a critical organ, bleeding requiring transfusion of red blood cells, and bleeding leading to a drop in hemoglobin levels. Fatal bleeding was ranked of highest relevance followed by bleeding leading to re-operation and bleeding affecting a critical organ. Responders appeared to be more concerned by bleeding that requires re-operation than major bleeds resulting in hemoglobin drops or those that require management by red blood cell transfusions.

Across the participating countries, the hemoglobin-drop threshold for defining major bleeding, as considered relevant by the responding physicians, varied from 4.06 g/dl in the UK to 6.57 g/dl in Spain. The thresholds for relevance in other countries were 6.16 g/dl in France, 5.06 g/dl in Germany, and 4.29 g/dl in the USA. The relevant threshold number of units of red blood cell transfusions that were

considered to define a major bleeding event varied between countries, from 2.36 units in the USA to 3.23 units in the UK. The thresholds for relevance in other countries were 3.06 units in France, 3.00 units in Germany, and 2.56 units in Spain.

In response to a question regarding how closely orthopedic surgeons and anesthesiologists read the detailed definitions for major bleeding included in publications reporting the results of clinical trials, fewer than half of all responders said they would usually read these parts of the article (Fig. 4). Less than 35% of responders consider bleeding definitions to be provided clearly within clinical study publications.

Efficacy and safety data in determining thromboprophylaxis choice

When given a choice between a thromboprophylactic agent offering reduced bleeding and similar VTE prevention to current anticoagulants, or an agent with better VTE

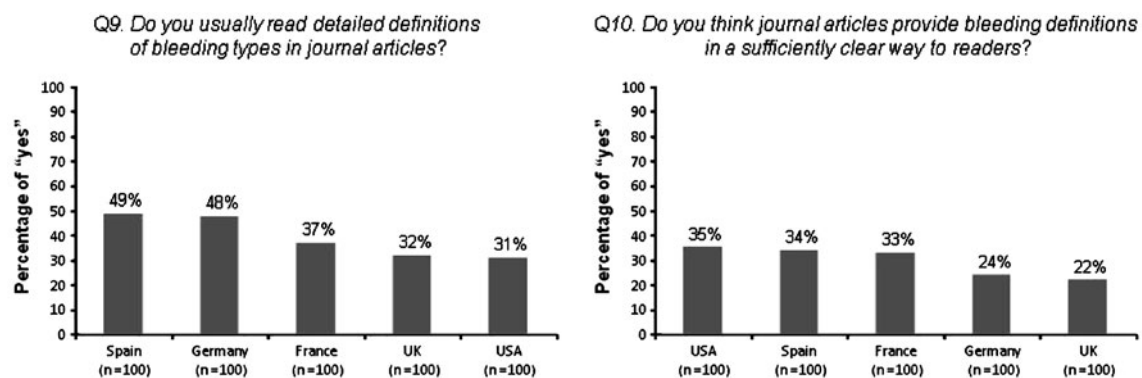
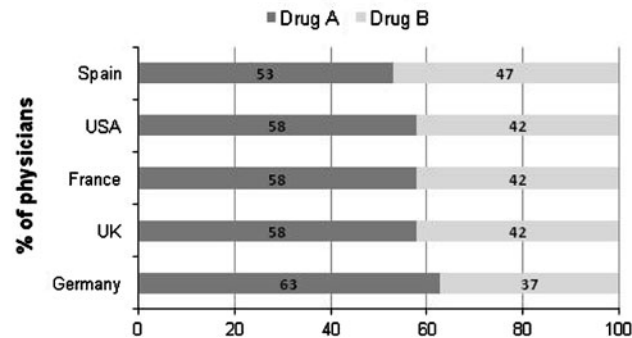


Fig. 4 Descriptions of bleeding definitions within clinical trial publications

**Fig. 5** The comparative role for improved venous thromboembolism (VTE) prevention and bleeding rates when determining choice of anticoagulant

Q13. If you had to choose between these 2 agents, which would you use for VTE prophylaxis:

Drug A: Reduced bleeding rate compared with current anticoagulants and same level of VTE prevention  
 Drug B: Better VTE prevention compared with current anticoagulants with the same bleeding rate



prevention and similar rates of bleeding to current anticoagulants, over 50% of responders would favor the use of a drug associated with reduced bleeding rates (Fig. 5).

## Discussion

The findings of our survey of practicing orthopedic surgeons highlight that a large proportion of surgeons in Europe and the USA continue to have concerns about surgical-site bleeding associated with the use of VTE thromboprophylaxis. Levels of concern about surgical-site bleeding far outweigh concerns about extra-surgical-site bleeds. Survey responders considered increases in surgical-site bleeding to likely adversely affect patient outcomes—potentially leading to longer in-patient stays and more protracted and difficult post-operative physiotherapy. The survey identified that bleeding requiring re-operation was a concern for this group of physicians, the majority of whom were orthopedic surgeons.

Physician surveys offer unique insights into “real life” practices, and the concerns and opinions held by surgeons involved in everyday patient management. Our survey highlights that there appears to be a disconnect between the endpoints that are reported in clinical studies of different agents for VTE prophylaxis, and “real life” concerns regarding the types of major bleeding and definitions of major bleeding held by practicing orthopedic surgeons.

The development of several new anticoagulant agents in the setting of VTE prevention in major orthopedic surgery patients, has increased the available therapeutic choices in this patient group. Although the efficacy of new agents has typically been compared with LMWH prophylaxis and evaluated using recognized VTE endpoints, there has been criticism that clinical trial programs of new agents have applied different definitions of bleeding risk, making

comparisons of safety profiles between different agents difficult [11]. Specifically, in the rivaroxaban Phase III trial program, surgical-site bleeding that was associated with a decrease in hemoglobin level of  $>2$  g/dL or leading to transfusion of  $\geq 2$  units of whole blood or packed cells was not included within the definition of major bleeding [2–5]. The inclusion of bleeding requiring re-operation within the definition of major bleeding in the rivaroxaban Phase III trials is in line with the results of this survey showing physicians’ concern regarding this type of bleeding. However, the omission of surgical-site bleeding in the rivaroxaban Phase III trial program results in under-reporting of major bleeding rates, even if such papers separately detail the rates of surgical-site bleeding [11]. Indeed, the need for consistency in the reporting of safety outcomes in clinical trials has been the focus of recent discussion in the literature, both regarding VTE prevention and anticoagulants, and more broadly with regards to safety data reporting from randomized controlled trials [11, 13, 14]. In an attempt to standardize the definition of major bleeding used in clinical studies, the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis has recently recommended a definition of major bleeding to be used in surgical clinical studies [15]. Surgical-site bleeding that requires re-operation and surgical-site bleeding that is unexpected, prolonged, and/or sufficiently large to cause hemodynamic instability (as assessed by the surgeon) are included within the suggested major-bleeding definition, emphasizing the importance of these types of bleeding in the surgical population.

The findings of the present survey seem to further emphasize the relevance of including surgical-site bleeding within the major-bleeding definition for patients undergoing orthopedic surgery. Responders all rated surgical-site bleeding as the type of bleeding and the site of major

bleeding of concern, with relevance to patient recovery and outcome. The survey also highlights that when working physicians review the available literature on anticoagulants, they often do not pay full attention to the definitions applied to reported rates of major bleeding. The exclusion of surgical-site bleeding from the definition of major bleeding and, in more general terms, the inadequate or inconsistent reporting of harm in clinical trials, may impact the interpretation of safety results and alter the reader's perception of the benefit-to-harm profile of specific therapies. This, in turn, affects the ability to effectively review the available evidence and make consistently informed decisions regarding therapy choice for any given patient [13, 14].

Clearly, the level of concern shown by orthopedic surgeons about bleeding complications may reflect the situations in which they find themselves responsible for dealing with, in terms of either a bleeding event or adverse event. The survey showed that this group of physician-responders—who were mainly surgeons—had concerns over bleeding that required re-operation. It would be interesting to have the views of other physicians involved in patient care, such as anesthesiologists and those involved in post-operative patient care, in order to determine if they would also rank bleeding concerns differently from those of the surgeons. Viewpoints on what constitutes major bleeding clearly differ, as even within this sample of physicians from five different countries, it was seen that threshold for transfusion varied from country to country. A review of the findings from the survey in France, where half of all responders were surgeons and half anesthesiologists (data not shown), suggests that anesthesiologists are more concerned than surgeons about bleedings indicated by a fall in hemoglobin levels and patient requirement for transfusion. This may possibly reflect their own professional responsibilities within the patient-care pathway.

Our data show that in all countries, except in Germany, an increase of surgical-site bleeding and the occurrence of surgical-site bleeding are expected to prolong patients' hospital stay and to complicate post-operative rehabilitation. This view is supported by evidence from a US hospital database study that shows that major bleeding after orthopedic surgery has clinical and economic consequences [16]. In addition, this US hospital database study found that major bleeding, defined as fatal bleeding, non-fatal bleeding at critical site, re-operation due to bleeding, and overt bleeding with bleeding index  $\geq 2$ , increased the length of hospital stay by a mean of 1.8 days and increased hospital charges by over US \$7500 [16].

When comparing the country differences in concern regarding bleeding and its impact on patient outcome, it is important to bear in mind the influences on perception that relate to different medical systems. This survey included

viewpoints from European countries where healthcare is predominantly state-funded, and viewpoints from the USA where there is a higher rate of privately funded healthcare. Cultural differences are also likely to affect the concerns expressed by physicians from different countries. The survey largely focused on surgeons' views on bleeding risk, assuming a certain belief that VTE prevention using thromboprophylactic therapies is an accepted part of the management of patients undergoing major orthopedic surgery. The growing medico-legal requirement of employing effective VTE prevention in at-risk patients is recognized in the medical literature [17], but there is less current literature regarding the legal pressure and cases concerning bleeding risks associated with VTE thromboprophylaxis. The medical literature provides some insights into patient perspectives and viewpoints regarding anticoagulant therapy, and suggests that patients' views on therapy are affected by inherent negative perceptions and attitudes, more than their risk for bleeding [18, 19]. However, much of the available literature on patient views relates to chronic anticoagulant therapy or use of vitamin K antagonists. A recently devised patient perception questionnaire on anticoagulant therapy has been developed in patients at VTE risk and may be used by physicians to get insights into the benefit-to-harm profile of therapies that concern and interest patients [20].

A number of potential limitations may affect the results of this survey. Responder rates to the survey were low (12–19% across countries); however, these rates were within the margins recorded for studies describing the results of surveys (responder rates usually between 10% and 20%). Although the survey questions were translated into the respective languages of the countries included, orthopedic surgeons may have incorrectly interpreted the survey questions. In addition, although we tried to have a global overview of physicians' perceptions by including physicians from four main European countries and the USA, any extrapolation to other countries than the ones presented here are limited. Country-by-country comparisons of this survey may be also limited by the inclusion of both anesthesiologists and orthopedic surgeons in France versus only orthopedic surgeons in the other countries.

In conclusion, our international survey highlights that physicians have concerns regarding surgical-site bleeding associated with VTE thromboprophylaxis in those patients undergoing major orthopedic surgery. In particular, there are concerns that an increase in surgical-site bleeding may lead to re-operation and impact the patient rate of recovery. There is a disconnect between the definitions of major bleeding that surgeons would apply to describe bleeding associated with VTE thromboprophylaxis, and the definitions customarily used in the literature and in recent clinical trials assessing the safety of anticoagulant agents.

Misperceptions regarding the benefit-to-harm profiles of thromboprophylactic therapies mean that patients may be mistreated, when physicians seek to choose the most suitable thromboprophylactic agent for patients at risk for post-operative VTE.

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