Conflict of Interest in the Assessment of Thromboprophylaxis After Total Joint Arthroplasty

A Systematic Review

Young-Kyun Lee, MD, Chin Youb Chung, MD, Kyung-Hoi Koo, MD, Kyoung Min Lee, MD, Hyung-Min Ji, MD, and Moon Seok Park, MD

Investigation performed at the Department of Orthopaedic Surgery, Seoul National University Bundang Hospital, Seoul, South Korea

Background: The choice of modalities for thromboprophylaxis after total joint arthroplasty is controversial. To address this issue, an evidence-based review of previous studies was performed. The characteristics of the studies selected for review can affect the final conclusion of an evidence-based review. One such characteristic, financial conflict of interest related to medical research, is a widespread concern. The purpose of the present study was to determine what proportion of studies on thromboprophylaxis after total joint arthroplasty were sponsored by industry and whether the assessments of thromboprophylaxis after total joint arthroplasty were associated with industry support.

Methods: We searched PubMed for prospective, original, English-language studies, published from 2004 to 2010, on thromboprophylaxis after total joint arthroplasty. The funding sources of the articles were reviewed, and qualitative conclusions regarding the modality of interest for thromboprophylaxis after total joint arthroplasty were classified as being favorable, neutral, or unfavorable.

Results: Seventy-one eligible articles were identified; fifty-two were funded by industry, and fourteen were not. The other five studies did not include information about the funding source. A significant association was observed between the funding source and qualitative conclusions ($p = 0.033$). Only two (3.8%) of the fifty-two industry-sponsored studies had unfavorable conclusions, whereas three (21.4%) of the fourteen non-industry-sponsored studies indicated that, depending on the clinical scenario, the modality examined was neither effective nor safe.

Conclusions: Most studies on thromboprophylaxis after total joint arthroplasty are sponsored by industry. Moreover, the qualitative conclusions in those studies are favorable to the use of the sponsored prophylactic agent.

Several modalities, including aspirin, vitamin K antagonists, low molecular weight heparins, pentasaccharides, direct thrombin inhibitors, factor Xa inhibitors, and pneumatic compression devices, have been evaluated for venous thromboprophylaxis after total joint arthroplasty. Furthermore, the efficacy and safety of these modalities, and the indications for their use, have become controversial, partly because of the issuance of several guidelines regarding venous thromboprophylaxis after total joint arthroplasty, such as those by the American College of Chest Physicians (ACCP), the American Academy of Orthopaedic Surgeons (AAOS), and the National Institute for Health and Clinical Excellence (NICE)[1-3].

Disclosure: None of the authors received payments or services, either directly or indirectly (i.e., via his or her institution), from a third party in support of any aspect of this work. None of the authors, or their institution(s), have had any financial relationship, in the thirty-six months prior to submission of this work, with any entity in the biomedical arena that could be perceived to influence or have the potential to influence what is written in this work. Also, no author has had any other relationships, or has engaged in any other activities, that could be perceived to influence or have the potential to influence what is written in this work. The complete **Disclosures of Potential Conflicts of Interest** submitted by authors are always provided with the online version of the article.

A commentary by Henry D. Clarke, MD, is linked to the online version of this article at jbjs.org.

In accordance with evidence-based medicine principles, each guideline-drafting committee systematically reviewed well-designed or qualified randomized controlled trials, which were methodologically considered to be sources of high-quality evidence[1-3]. However, although these evidence-based guidelines or systematic reviews provided high-quality evidence, they could have been affected by the characteristics of the selected studies[4].

A financial conflict of interest can bias the results of medical or orthopaedic research[5-8]. Several studies have demonstrated that industry funding is common in research and that the outcomes might be influenced[5,6,9-12]. However, we are not aware of any previous studies on the topic of conflict of interest related to thromboprophylaxis after total joint arthroplasty.

In the present study, we sought to determine which proportion of prospectively designed original studies on thromboprophylaxis after total joint arthroplasty were industry-sponsored and whether the qualitative conclusions by the study authors about the modality of thromboprophylaxis was associated with the financial sponsorship of the studies.

Materials and Methods

The present study was exempted from institutional review board review because it did not involve human subjects.

Criteria for Studies

The present systematic review included studies that (1) were published as original articles in the English-language literature from 2004 to 2010, (2) included patients managed with total hip or knee arthroplasty, (3) evaluated the prevention and control of venous thromboembolism, and (4) had a prospective design.

Search Strategy

Studies were identified with a PubMed search (http://www.ncbi.nlm.nih.gov/pubmed). The following search terms were used for the literature search of the PubMed database: (1) ("hip"[MeSH Terms] OR "hip"[All Fields]) OR ("knee"[MeSH Terms] OR "knee"[All Fields] OR "knee joint"[MeSH Terms] OR ("knee"[All Fields] AND "joint"[All Fields]) OR "knee joint"[All Fields]), (2) ("thromboembolism/prevention and control"[MeSH Terms] OR "venous thrombosis/prevention and control"[MeSH Terms] OR "thromboprophylaxis"[All Fields]), and (3) "english"[language]. The identified studies were then filtered to limit the search to publications from 2004 to 2010.

Selection of Studies

The studies that had been identified during the PubMed search were screened, and those that had been published in journals that did not require disclosure of conflicts of interest were excluded. The full text of the remaining articles was then retrieved. One of the authors (Y.-K.L.) reviewed the full articles to determine whether thromboprophylaxis after total joint arthroplasty had been reported. Letters, editorials, correspondence, and review articles were excluded. Finally, only original studies with a prospective design were selected.

Data Collection and Analysis

Two authors (Y.-K.L., K.M.L.) independently reviewed each study with regard to the authors, year of publication, country, study design (randomized controlled trial, cohort, case series, or epidemiological study), total number of patients evaluated at the time of the latest follow-up, type of arthroplasty, thromboprophylaxis modality used in the study and control groups, qualitative conclusions regarding the modality of interest, and financial sponsorship. When necessary, the authors of the studies or the editors of the journals were contacted by e-mail to identify sponsorship.

Most studies evaluated several primary and/or secondary outcomes in efficacy or safety. The primary efficacy and safety outcomes from each study were evaluated to rate the qualitative conclusions.

The raters used all information available, including the quantitative results such as significance and numerical differences. In studies with active comparators, the raters examined whether the quantitative results for the primary efficacy outcome were based on a significant difference, with use of a p value of <0.05, which was confirmed by calculating the odds ratio with the 95% confidence interval (CI) between both groups. On the basis of these quantitative results and the authors' key sentence in the conclusion or in the last paragraph of the Discussion, the qualitative conclusions for the modality of interest were rated as favorable (the modality of interest was "more effective," "more safe," "superior," or "favorable" compared with the control), neutral (the modality of interest was "effective," "may be effective," or "is safe" compared with the control), or unfavorable (the modality of interest was "less effective" or "less safe" compared with the control), as described elsewhere[9,13]. The statistical results were examined further to determine if the primary hypothesis of the study was supported and whether a noninferiority test for the interested modality was planned as the primary end point. Studies for dose adjustment of a new drug were considered to have a neutral qualitative conclusion. In studies without an active comparator, the raters evaluated the qualitative conclusion in terms of the strength of the recommendation or need for the modality for thromboprophylaxis after total joint arthroplasty. In case series, the raters based their judgments on the strength of the recommendations made in the conclusion or in the last paragraph of the Discussion. Epidemiological observational studies that did not investigate an intervention for thromboprophylaxis were considered to be favorable to the need for thromboprophylaxis if the prevalence of venous thromboembolism was high and unfavorable if the prevalence of venous thromboembolism was low.

If the two raters (Y.-K.L., K.M.L.) disagreed over the qualitative conclusions of the article, the final decision was made by a third rater (M.S.P.)[9].

With regard to sponsorship, each study was categorized as being sponsored or unidentifiable. In the sponsored studies, the study was categorized as industry-sponsored or non-industry-sponsored. A study was industry-sponsored if at least one author was listed as an employee of a pharmaceutical or medical device company or an acknowledgment was made concerning the financial support of the pharmaceutical or medical device company. A study was considered to be non-industry-sponsored if it was funded by a non-industry entity (for example, a government agency, nonprofit foundation, or academic institution) or if it was not funded[13].

Statistical Analysis

An independent t test was used to analyze the relationship between the funding source and the total number of evaluated patients. The Fisher exact test was used to analyze the relationship between the funding source and categorical variables, including author affiliations (all academic or at least one pharmaceutical company or consulting firm employee), study design (with or without a comparator), geographical location of the corresponding author (Western or non-Western), and department of the corresponding author (orthopaedic or nonorthopaedic). The chi-square test was used to analyze the relationship between the funding source and the qualitative conclusion (favorable, neutral, or unfavorable) in a 2×3 table. The level of significance was set at $p < 0.05$. After the authors of the studies or the editors of the journals had been contacted to identify any sponsorship, the unidentifiable studies were not included in the relationship analysis.

Source of Funding

There was no external funding source for this investigation.

Results

A search of the PubMed database identified a total of 517 published articles that pertained to thromboprophylaxis after total joint arthroplasty (Fig. 1). Of these 517 studies, sixty-two

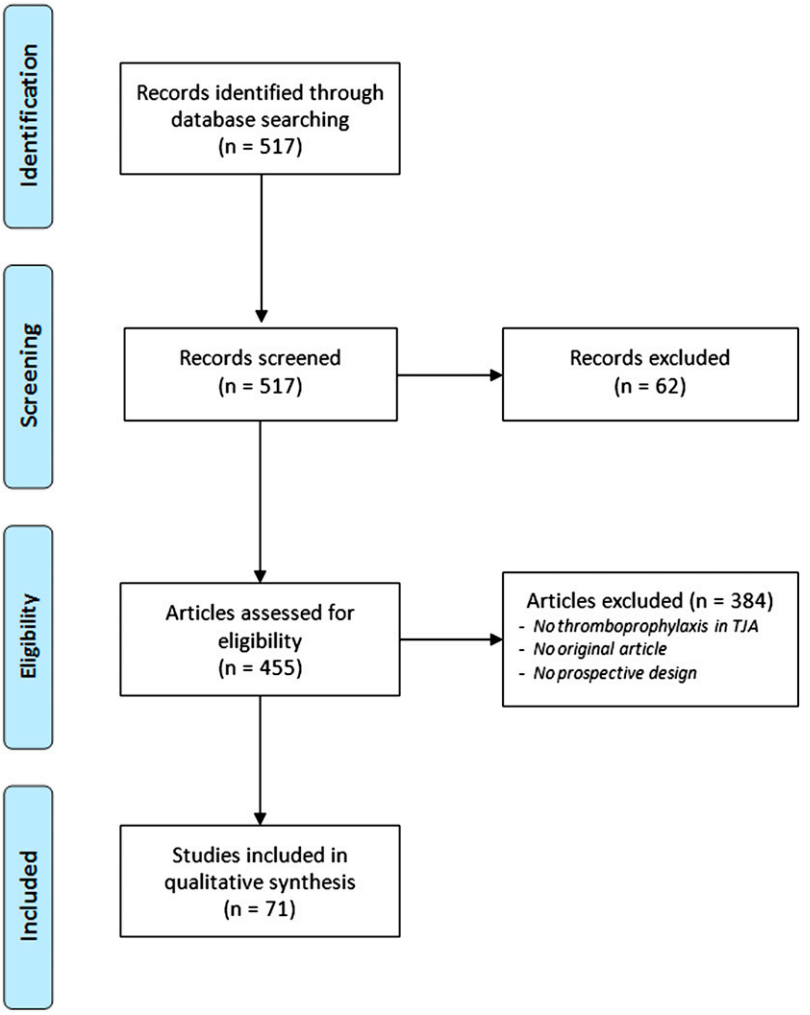

Fig. 1

Flowchart showing the search strategy to identify studies of thromboprophylaxis after total joint arthroplasty (TJA).

were excluded because the corresponding journals did not require a disclosure of conflict of interest and 384 were excluded because they were not prospective original articles on thromboprophylaxis after total joint arthroplasty. The remaining seventy-one studies were analyzed (see Appendix)[14-84]. In five of the seventy-one studies, sponsorship could not be identified even after contact with the authors or editors. Fifty-two (78.8%) of the remaining sixty-six studies were funded by pharmaceutical or medical device companies. Most of these industry-sponsored studies were performed in Western countries, that is, Sweden (ten studies), the United States (seven), Denmark (seven), Canada (six), Germany (six), France (three), Italy (three), the United Kingdom (two), Spain (two), and Belgium (one).

The qualitative conclusions showed a significant association with the funding source ($p = 0.033$) (Table I). Only two (3.8%) of the fifty-two industry-sponsored studies had unfavorable conclusions, whereas three (21.4%) of the fourteen non-industry-sponsored studies, depending on the clinical scenario, had unfavorable conclusions. All of the authors of the non-industry-sponsored studies had academic affiliations, whereas thirty-four (65.4%) of the fifty-two industry-sponsored studies had at least one author who was affiliated with a pharmaceutical or medical device company ($p < 0.001$). Of the eighteen industry-sponsored studies with all academic authors, no study had an unfavorable conclusion regarding thromboprophylaxis after total joint arthroplasty. Industry-sponsored studies were more likely to have a comparator (88.5%, forty-six of fifty-two) than non-industry-sponsored studies (50%, seven of fourteen) ($p = 0.004$) and included larger numbers of evaluated patients ($p = 0.001$) (Table I). Of the forty-six industry-sponsored studies with a comparator, only two had unfavorable conclusions regarding the modality examined (see Appendix). More industry-sponsored studies were performed in Western countries than in non-Western countries ($p = 0.029$).

Of the forty-six industry-sponsored studies with a comparator, thirty-seven (80.4%) had results that confirmed the primary hypothesis. In addition, a noninferiority test was planned as the primary end point in thirteen industry-sponsored

TABLE I Study Characteristics and Conclusions According to Funding Source

	Industry-Sponsored (N = 52)	Non-Industry-Sponsored (N = 14)	P Value
Number of evaluated patients	1109.3 ± 1147.2	360.2 ± 510.3	0.001
Author *(no. of studies)*			<0.001
All academic	18	14	
≥1 company employee	34	0	
Region or country *(no. of studies)*			0.029
Western	47	9	
Non-Western	5	5	
Department of corresponding author *(no. of studies)*			0.195
Orthopaedics	33	12	
Nonorthopaedics	19	2	
Design of study *(no. of studies)*			0.004
With comparator	46	7	
Without comparator	6	7	
Qualitative conclusions *(no. of studies)*			0.033
Favorable	24	8	
Neutral	26	3	
Unfavorable	2	3	

TABLE II Analysis of Hypothesis and Statistics in the Fifty-Three Studies with Active Comparators

	Industry-Sponsored (N = 46)	Non-Industry-Sponsored (N = 7)	P Value
Hypothesis supported *(no. of studies)*			0.626
Yes	37	5	
No	9	2	
Statistical test *(no. of studies)*			0.660
Superiority test	33	6	
Noninferiority test	13	1	

studies and in only one non-industry-sponsored study (Table II).

Discussion

The present study was designed to examine the financial conflict of interest in studies of thromboprophylaxis after total joint arthroplasty. The results demonstrated that the majority (79%) of studies of thromboprophylaxis after total joint arthroplasty were sponsored by industry and that the qualitative conclusions by the authors of these studies were associated with industry sponsorship. The authors of nineteen (41.3%) of the forty-six industry-sponsored comparative studies concluded that the sponsored modality had a favorable effect or was safer than the other modalities (see Appendix).

There are several possible explanations for these findings. First, there might have been publication bias[10-12]. Regardless of the funding source, medical research studies with positive results are published more frequently than those with negative results[10-12]. Second, companies may collaborate directly with academic researchers by developing study protocols or indirectly by devising the outcome variables. In the present study of thromboprophylaxis after total joint arthroplasty, we found that an employee of the sponsoring company was included as a coauthor in 65.4% of the industry-sponsored studies. Industry-sponsored studies may be specially designed to confirm the suspected advantages of the modality that the particular company developed. Indeed, among the fifty-three studies with a comparator, thirteen of the forty-six industry-sponsored studies used a noninferiority test for the primary end point, compared with only one of the seven non-industry-sponsored studies (Table II). Third, a company can influence researchers in several types of sponsorships, such as unrestricted research grants, educational funds, consultancies, or travel grants for scientific meetings[85], which can cause unconscious bias in researchers[12].

The present systematic review had several limitations. First, only direct funding of a study was considered as a financial conflict of interest. Indirect funding, which is more difficult to define, would be potentially associated with the authors' conclusion. Second, the modalities used for thromboprophylaxis after total joint arthroplasty were heterogeneous (for example, low molecular weight heparin, warfarin, direct thrombin inhibitor, factor Xa inhibitor, and pneumatic compression device). Third, only the primary efficacy or safety outcome of the various modalities was rated. Almost all of the selected studies included asymptomatic deep-vein thrombosis as a primary outcome variable, which has been criticized by many orthopaedic surgeons who have emphasized that a symptomatic pulmonary embolism should be used as an outcome variable instead because it is the target

of thromboprophylaxis after total joint arthroplasty. Wound-associated problems, which were considered secondary outcome variables in most studies, are also important to orthopaedic surgeons with responsibility for total joint arthroplasty and orthopaedic patients. This priority in selecting the outcome variables might also be influenced by industry companies sponsoring the studies. Fourth, the number of non-industry-funded studies was small, and therefore our statistical analysis was sensitive to the conclusion (favorable, neutral, or unfavorable) of non-industry-funded studies. That is, the p values were more dependent on the conclusions of the non-industry-funded studies than on those of the industry-funded studies. In addition, there was no sponsorship information in five of the seventy-one studies. Studies with an unidentified conflict of interest could affect the statistical results of the present study, although attempts were made to contact the corresponding authors of the articles or the editors of the journals. If the five studies with unidentifiable funding were funded by industry, the qualitative conclusions still showed a significant relationship with the funding source ($p = 0.022$). On the other hand, if the five studies with unidentifiable funding were not funded by industry, the results in this study would not be significant ($p = 0.136$). However, the average impact factor (and standard deviation) of the journals in which the fifty-six articles with identifiable funding were published (7.5 ± 12.0) was significantly higher than that of the journals in which the five studies with unidentifiable funding were published (1.1 ± 0.7), and the analysis without these five articles could be justified.

During the selection of the studies, it was found that several journals did not require disclosure of any conflict of interest for publication, and, of the journals requiring a conflict of interest statement, some did not strictly enforce their conflict of interest policy. In terms of disclosure, journal readers need to be able to easily identify potential conflicts, particularly in medical research that may be influenced by sponsorship.

Despite these limitations, the present study demonstrated that a potential conflict of interest was common, with industry funding being provided for fifty-two (78.8%) of the sixty-six research articles assessing thromboprophylaxis after total joint arthroplasty that qualified for the present systematic review. Furthermore, this conflict of interest could account for the conclusions favoring more aggressive thromboprophylaxis, which can be included in evidence-based guidelines.

Although sponsorship of these studies could have affected the assessment of thromboprophylaxis after total joint arthroplasty, blaming the industry-sponsored studies is probably not practical because these companies provide valuable resources for well-designed studies in research[86]. Furthermore, well-designed studies, whether industry-sponsored or not, provide valuable evidence-based information on thromboprophylaxis after total joint arthroplasty.

However, on the basis of finding in the present systematic review that qualitative conclusions in studies on thromboprophylaxis after total joint arthroplasty were associated with the funding source, surgeons should be aware of an industry-related conflict of interest regarding a report on the efficacy or safety of a thromboprophylaxis modality after total joint arthroplasty.

Appendix

(eA) A table showing the characteristics of seventy-one studies of thromboprophylaxis after total joint arthroplasty is available with the online version of this article as a data supplement at jbjs.org. ■

NOTE: The authors thank Soyeon Ahn and Jaebong Lee for statistical advice and Mi Seon Ryu for assistance in data collection.

Young-Kyun Lee, MD
Chin Youb Chung, MD
Kyung-Hoi Koo, MD
Kyoung Min Lee, MD
Hyung-Min Ji, MD
Moon Seok Park, MD
Department of Orthopaedic Surgery,
Seoul National University Bundang Hospital,
166 Gumi-ro, Bundang-Gu, Sungnam-si,
Gyeonggi-do 463-707, South Korea.
E-mail address for M.S. Park: pmsmed@gmail.com

References

1. Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, Ray JG. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126(3 Suppl):338S–400S.

2. Johanson NA, Lachiewicz PF, Lieberman JR, Lotke PA, Parvizi J, Pellegrini V, Stringer TA, Tornetta P 3rd, Haralson RH 3rd, Watters WC 3rd. American Academy of Orthopaedic Surgeons clinical practice guideline on: Prevention of symptomatic pulmonary embolism in patients undergoing total hip or knee arthroplasty. J Bone Joint Surg Am. 2009;91:1756–7.

3. Hill J, Treasure T. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in inpatients having surgery: summary of NICE guidance. BMJ. 2007;334:1053–4.

4. Eikelboom JW, Karthikeyan G, Fagel N, Hirsh J. American Association of Orthopedic Surgeons and American College of Chest Physicians guidelines for venous thromboembolism prevention in hip and knee arthroplasty differ: what are the implications for clinicians and patients? Chest. 2009;135:513–20.

5. Zuckerman JD, Prasarn M, Kubiak EN, Koval KJ. Conflict of interest in orthopaedic research. J Bone Joint Surg Am. 2004;86:423–8.

6. Okike K, Kocher MS, Mehlman CT, Bhandari M. Conflict of interest in orthopaedic research. An association between findings and funding in scientific presentations. J Bone Joint Surg Am. 2007;89:608–13.

7. Stelfox HT, Chua G, O'Rourke K, Detsky AS. Conflict of interest in the debate over calcium-channel antagonists. N Engl J Med. 1998;338:101–6.

8. Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. JAMA. 2003;289:454–65.

9. Jang S, Chae YK, Haddad T, Majhail NS. Conflict of interest in economic analyses of aromatase inhibitors in breast cancer: a systematic review. Breast Cancer Res Treat. 2010;121:273–9.

10. Bero LA, Rennie D. Influences on the quality of published drug studies. Int J Technol Assess Health Care. 1996;12:209–37.

11. Callaham ML, Wears RL, Weber EJ, Barton C, Young G. Positive-outcome bias and other limitations in the outcome of research abstracts submitted to a scientific meeting. JAMA. 1998;280:254–7.

12. Friedberg M, Saffran B, Stinson TJ, Nelson W, Bennett CL. Evaluation of conflict of interest in economic analyses of new drugs used in oncology. JAMA. 1999;282:1453–7.

13. Baker CB, Johnsrud MT, Crismon ML, Rosenheck RA, Woods SW. Quantitative analysis of sponsorship bias in economic studies of antidepressants. Br J Psychiatry. 2003;183:498–506.

14. Lachiewicz PF, Kelley SS, Haden LR. Two mechanical devices for prophylaxis of thromboembolism after total knee arthroplasty. A prospective, randomised study. J Bone Joint Surg Br. 2004;86:1137–41.

15. Silbersack Y, Taute BM, Hein W, Podhaisky H. Prevention of deep-vein thrombosis after total hip and knee replacement. Low-molecular-weight heparin in combination with intermittent pneumatic compression. J Bone Joint Surg Br. 2004; 86:809–12.

16. Eriksson BI, Dahl OE, Ahnfelt L, Kälebo P, Stangier J, Nehmiz G, Hermansson K, Kohlbrenner V. Dose escalating safety study of a new oral direct thrombin inhibitor, dabigatran etexilate, in patients undergoing total hip replacement: BISTRO I. J Thromb Haemost. 2004;2:1573–80.

17. Pitto RP, Hamer H, Heiss-Dunlop W, Kuehle J. Mechanical prophylaxis of deep-vein thrombosis after total hip replacement a randomised clinical trial. J Bone Joint Surg Br. 2004;86:639–42.

18. Eriksson BI, Dahl OE, Büller HR, Hettiarachchi R, Rosencher N, Bravo ML, Ahnfelt L, Piovella F, Stangier J, Kälebo P, Reilly P; BISTRO II Study Group. A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: the BISTRO II randomized trial. J Thromb Haemost. 2005;3:103–11.

19. Kearon C, Comp P, Douketis J, Royds R, Yamada K, Gent M. Dose-response study of recombinant human soluble thrombomodulin (ART-123) in the prevention of venous thromboembolism after total hip replacement. J Thromb Haemost. 2005;3: 962–8.

20. Leizorovicz A, Turpie AG, Cohen AT, Wong L, Yoo MC, Dans A; SMART Study Group. Epidemiology of venous thromboembolism in Asian patients undergoing major orthopedic surgery without thromboprophylaxis. The SMART study. J Thromb Haemost. 2005;3:28–34.

21. Colwell CW Jr, Berkowitz SD, Lieberman JR, Comp PC, Ginsberg JS, Paiement G, McElhattan J, Roth AW, Francis CW; EXULT B Study Group. Oral direct thrombin inhibitor ximelagatran compared with warfarin for the prevention of venous thromboembolism after total knee arthroplasty. J Bone Joint Surg Am. 2005;87:2169–77.

22. Piovella F, Wang CJ, Lu H, Lee K, Lee LH, Lee WC, Turpie AG, Gallus AS, Planès A, Passera R, Rouillon A; AIDA investigators. Deep-vein thrombosis rates after major orthopedic surgery in Asia. An epidemiological study based on postoperative screening with centrally adjudicated bilateral venography. J Thromb Haemost. 2005;3:2664–70.

23. Turpie AG, Fisher WD, Bauer KA, Kwong LM, Irwin MW, Kälebo P, Misselwitz F, Gent M; OdiXa-Knee Study Group. BAY 59-7939: an oral, direct factor Xa inhibitor for the prevention of venous thromboembolism in patients after total knee replacement. A phase II dose-ranging study. J Thromb Haemost. 2005;3:2479–86.

24. Bonneux IM, Bellemans J, Fabry G. Evaluation of wound healing after total knee arthroplasty in a randomized prospective trial comparing fondaparinux with enoxaparin. Knee. 2006;13:118–21.

25. Colwell CW Jr, Kwong LM, Turpie AG, Davidson BL. Flexibility in administration of fondaparinux for prevention of symptomatic venous thromboembolism in orthopaedic surgery. J Arthroplasty. 2006;21:36–45.

26. Eriksson BI, Borris LC, Dahl OE, Haas S, Huisman MV, Kakkar AK, Muehlhofer E, Dierig C, Misselwitz F, Kälebo P; ODIXa-HIP Study Investigators. A once-daily, oral, direct Factor Xa inhibitor, rivaroxaban (BAY 59-7939), for thromboprophylaxis after total hip replacement. Circulation. 2006;114:2374–81.

27. Haas S, Breyer HG, Bacher HP, Fareed J, Misselwitz F, Victor N, Weber J; ECHOS Trial Group. Prevention of major venous thromboembolism following total hip or knee replacement: a randomized comparison of low-molecular-weight heparin with unfractionated heparin (ECHOS Trial). Int Angiol. 2006;25:335–42.

28. Senaran H. Acaroğlu E, Ozdemir HM, Atilla B. Enoxaparin and heparin comparison of deep vein thrombosis prophylaxis in total hip replacement patients. Arch Orthop Trauma Surg. 2006;126:1–5.

29. Eriksson BI, Borris L, Dahl OE, Haas S, Huisman MV, Kakkar AK, Misselwitz F, Kälebo P; ODIXa-HIP Study Investigators. Oral, direct Factor Xa inhibition with BAY 59-7939 for the prevention of venous thromboembolism after total hip replacement. J Thromb Haemost. 2006;4:121–8.

30. Westrich GH, Bottner F, Windsor RE, Laskin RS, Haas SB, Sculco TP. VenaFlow plus Lovenox vs VenaFlow plus aspirin for thromboembolic disease prophylaxis in total knee arthroplasty. J Arthroplasty. 2006;21:139–43.

31. Eriksson BI, Borris LC, Dahl OE, Haas S, Huisman MV, Kakkar AK, Misselwitz F, Muehlhofer E, Kälebo P. Dose-escalation study of rivaroxaban (BAY 59-7939)—an oral, direct Factor Xa inhibitor—for the prevention of venous thromboembolism in patients undergoing total hip replacement. Thromb Res. 2007;120:685–93.

32. Lassen MR, Davidson BL, Gallus A, Pineo G, Ansell J, Deitchman D. The efficacy and safety of apixaban, an oral, direct factor Xa inhibitor, as thromboprophylaxis in patients following total knee replacement. J Thromb Haemost. 2007;5:2368–75.

33. Samama CM, Ravaud P, Parent F, Barré J, Mertl P, Mismetti P. Epidemiology of venous thromboembolism after lower limb arthroplasty: the FOTO study. J Thromb Haemost. 2007;5:2360–7.

34. Abad JI, Gómez-Outes A, Martínez-González J, Rocha E; Bemiparin 6 Hours After Surgery Study Group. A prospective observational study on the effectiveness and safety of bemiparin, first dose administered 6 h after knee or hip replacement surgery. Arch Orthop Trauma Surg. 2007;127:665–70.

35. Agnelli G, Haas S, Ginsberg JS, Krueger KA, Dmitrienko A, Brandt JT. A phase II study of the oral factor Xa inhibitor LY517717 for the prevention of venous thromboembolism after hip or knee replacement. J Thromb Haemost. 2007;5:746–53.

36. Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, Prins MH, Hettiarachchi R, Hantel S, Schnee J, Büller HR; RE-NOVATE Study Group. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. Lancet. 2007;370:949–56.

37. Leizorovicz A; SMART Venography Study Steering Committee. Epidemiology of post-operative venous thromboembolism in Asian patients. Results of the SMART venography study. Haematologica. 2007;92:1194–200.

38. Trocóniz IF, Tillmann C, Liesenfeld KH, Schäfer HG, Stangier J. Population pharmacokinetic analysis of the new oral thrombin inhibitor dabigatran etexilate (BIBR 1048) in patients undergoing primary elective total hip replacement surgery. J Clin Pharmacol. 2007;47:371–82.

39. Eisele R, Kinzl L, Koelsch T. Rapid-inflation intermittent pneumatic compression for prevention of deep venous thrombosis. J Bone Joint Surg Am. 2007;89: 1050–6.

40. Eriksson BI, Turpie AG, Lassen MR, Prins MH, Agnelli G, Kälebo P, Gaillard ML, Meems L; ONYX study group. A dose escalation study of YM150, an oral direct factor Xa inhibitor, in the prevention of venous thromboembolism in elective primary hip replacement surgery. J Thromb Haemost. 2007;5:1660–5.

41. Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, Kälebo P, Christiansen AV, Hantel S, Hettiarachchi R, Schnee J, Büller HR; RE-MODEL Study Group. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. J Thromb Haemost. 2007;5:2178–85.

42. Cohen AT, Skinner JA, Warwick D, Brenkel I. The use of graduated compression stockings in association with fondaparinux in surgery of the hip. A multicentre, multinational, randomised, open-label, parallel-group comparative study. J Bone Joint Surg Br. 2007;89:887–92.

43. Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, Misselwitz F, Turpie AG; RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med. 2008;358:2776–86.

44. Edwards JZ, Pulido PA, Ezzet KA, Copp SN, Walker RH, Colwell CW Jr. Portable compression device and low-molecular-weight heparin compared with low-molecular-weight heparin for thromboprophylaxis after total joint arthroplasty. J Arthroplasty. 2008;23:1122–7.

45. Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, Bandel TJ, Beckmann H, Muehlhofer E, Misselwitz F, Geerts W; RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med. 2008;358:2765–75.

46. Fuji T, Fujita S, Ochi T. Fondaparinux prevents venous thromboembolism after joint replacement surgery in Japanese patients. Int Orthop. 2008;32:443–51.

47. Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, Soglian AG, Pap AF, Misselwitz F, Haas S; RECORD2 Investigators. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. Lancet. 2008;372:31–9.

48. Lassen MR, Dahl O, Mismetti P, Zielske D, Turpie AG. SR123781A: a new once-daily synthetic oligosaccharide anticoagulant for thromboprophylaxis after total hip replacement surgery: the DRIVE (Dose Ranging Study in Elective Total Hip Replacement Surgery) study. J Am Coll Cardiol. 2008;51:1498–504.

49. Mueck W, Borris LC, Dahl OE, Haas S, Huisman MV, Kakkar AK, Kälebo P, Muelhofer E, Misselwitz F, Eriksson BI. Population pharmacokinetics and pharmacodynamics of once- and twice-daily rivaroxaban for the prevention of venous thromboembolism in patients undergoing total hip replacement. Thromb Haemost. 2008;100:453–61.

50. Mueck W, Eriksson BI, Bauer KA, Borris L, Dahl OE, Fisher WD, Gent M, Haas S, Huisman MV, Kakkar AK, Kälebo P, Kwong LM, Misselwitz F, Turpie AG. Population pharmacokinetics and pharmacodynamics of rivaroxaban—an oral, direct factor Xa inhibitor—in patients undergoing major orthopaedic surgery. Clin Pharmacokinet. 2008;47:203–16.

51. Otero-Fernández R, Gómez-Outes A, Martínez-González J, Rocha E, Fontcuberta J; Bemiparin Cooperative Study Group in Orthopaedic Patients. Evaluation of the effectiveness and safety of bemiparin in a large population of orthopedic patients in a normal clinical practice. Clin Appl Thromb Hemost. 2008;14:75–83.

52. Fuji T, Ochi T, Niwa S, Fujita S. Prevention of postoperative venous thromboembolism in Japanese patients undergoing total hip or knee arthroplasty: two randomized, double-blind, placebo-controlled studies with three dosage regimens of enoxaparin. J Orthop Sci. 2008;13:442–51.

53. Turpie AG, Lassen MR, Davidson BL, Bauer KA, Gent M, Kwong LM, Cushner FD, Lotke PA, Berkowitz SD, Bandel TJ, Benson A, Misselwitz F, Fisher WD; RECORD4

Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet. 2009;373:1673–80.

54. Turpie AG, Bauer KA, Davidson BL, Fisher WD, Gent M, Huo MH, Sinha U, Gretler DD; EXPERT Study Group. A randomized evaluation of betrixaban, an oral factor Xa inhibitor, for prevention of thromboembolic events after total knee replacement (EXPERT). Thromb Haemost. 2009;101:68–76.

55. Lassen MR, Dahl OE, Mismetti P, Destrée D, Turpie AG. AVE5026, a new hemisynthetic ultra-low-molecular-weight heparin for the prevention of venous thromboembolism in patients after total knee replacement surgery—TREK: a dose-ranging study. J Thromb Haemost. 2009;7:566–72.

56. RE-MOBILIZE Writing Committee, Ginsberg JS, Davidson BL, Comp PC, Francis CW, Friedman RJ, Huo MH, Lieberman JR, Muntz JE, Raskob GE, Clements ML, Hantel S, Schnee JM, Caprini JA. Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. J Arthroplasty. 2009;24:1–9.

57. Agnelli G, Eriksson BI, Cohen AT, Bergqvist D, Dahl OE, Lassen MR, Mouret P, Rosencher N, Andersson M, Bylock A, Jensen E, Boberg B; EXTEND Study Group. Safety assessment of new antithrombotic agents: lessons from the EXTEND study on ximelagatran. Thromb Res. 2009;123:488–97.

58. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. N Engl J Med. 2009;361:594–604.

59. Colwell CW Jr, Froimson MI, Mont MA, Ritter MA, Trousdale RT, Buehler KC, Spitzer A, Donaldson TK, Padgett DE. Thrombosis prevention after total hip arthroplasty: a prospective, randomized trial comparing a mobile compression device with low-molecular-weight heparin. J Bone Joint Surg Am. 2010;92:527–35.

60. Eriksson BI, Turpie AG, Lassen MR, Prins MH, Agnelli G, Kälebo P, Wetherill G, Wilpshaar JW, Meems L; ONYX-2 STUDY GROUP. Prevention of venous thromboembolism with an oral factor Xa inhibitor, YM150, after total hip arthroplasty. A dose finding study (ONYX-2). J Thromb Haemost. 2010;8:714–21.

61. Fuji T, Fujita S, Tachibana S, Kawai Y. A dose-ranging study evaluating the oral factor Xa inhibitor edoxaban for the prevention of venous thromboembolism in patients undergoing total knee arthroplasty. J Thromb Haemost. 2010;8:2458–68.

62. Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LM; ADVANCE-3 Investigators. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. N Engl J Med. 2010;363:2487–98.

63. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P; ADVANCE-2 investigators. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. Lancet. 2010;375:807–15.

64. Raskob G, Cohen AT, Eriksson BI, Puskas D, Shi M, Bocanegra T, Weitz JI. Oral direct factor Xa inhibition with edoxaban for thromboprophylaxis after elective total hip replacement. A randomised double-blind dose-response study. Thromb Haemost. 2010;104:642–9.

65. Weitz JI, Cao C, Eriksson BI, Fisher W, Kupfer S, Raskob G, Spaeder J, Turpie AG. A dose-finding study with TAK-442, an oral factor Xa inhibitor, in patients undergoing elective total knee replacement surgery. Thromb Haemost. 2010;104:1150–7.

66. Wang CJ, Wang JW, Weng LH, Hsu CC, Huang CC, Yu PC. Prevention of deep-vein thrombosis after total knee arthroplasty in Asian patients. Comparison of low-molecular-weight heparin and indomethacin. J Bone Joint Surg Am. 2004;86:136–40.

67. Pulido PA, Copp SN, Walker RH, Reden LM, Hardwick ME, Colwell CW Jr. The efficacy of a single daily dose of enoxaparin for deep vein thrombosis prophylaxis following total knee arthroplasty. Orthopedics. 2004;27:1185–7.

68. Westrich GH, Salvati EA, Sharrock N, Potter HG, Sánchez PM, Sculco TP. The effect of intraoperative heparin administered during total hip arthroplasty on the incidence of proximal deep vein thrombosis assessed by magnetic resonance venography. J Arthroplasty. 2005;20:42–50.

69. Bagaria V, Modi N, Panghate A, Vaidya S. Incidence and risk factors for development of venous thromboembolism in Indian patients undergoing major orthopaedic surgery: results of a prospective study. Postgrad Med J. 2006;82:136–9.

70. Gelfer Y, Tavor H, Oron A, Peer A, Halperin N, Robinson D. Deep vein thrombosis prevention in joint arthroplasties: continuous enhanced circulation therapy vs low molecular weight heparin. J Arthroplasty. 2006;21:206–14.

71. González Della Valle A, Serota A, Go G, Sorriaux G, Sculco TP, Sharrock NE, Salvati EA. Venous thromboembolism is rare with a multimodal prophylaxis protocol after total hip arthroplasty. Clin Orthop Relat Res. 2006;444:146–53.

72. Giannoni MF, Ciatti R, Capoccia L, Ruggiero M, Dauri M, Mariani PP. Total knee replacement: prevention of deep-vein thrombosis using pharmacological (low-molecular-weight heparin) and mechanical (intermittent foot sole pump system) combined prophylaxis. Preliminary results. Int Angiol. 2006;25:316–21.

73. Burnett RS, Clohisy JC, Wright RW, McDonald DJ, Shively RA, Givens SA, Barrack RL. Failure of the American College of Chest Physicians-1A protocol for Lovenox in clinical outcomes for thromboembolic prophylaxis. J Arthroplasty. 2007;22:317–24.

74. Asnis PD, Gardner MJ, Ranawat A, Leitzes AH, Peterson MG, Bass AR. The effectiveness of warfarin dosing from a nomogram compared with house staff dosing. J Arthroplasty. 2007;22:213–8.

75. Lachiewicz PF, Soileau ES. Mechanical calf compression and aspirin prophylaxis for total knee arthroplasty. Clin Orthop Relat Res. 2007;464:61–4.

76. Chandrasekaran S, Ariaretnam SK, Tsung J, Dickison D. Early mobilization after total knee replacement reduces the incidence of deep venous thrombosis. ANZ J Surg. 2009;79:526–9.

77. Barrellier MT, Lebel B, Parienti JJ, Mismetti P, Dutheil JJ, Vielpeau C; PROTHEGE study group; GETHCAM study group. Short versus extended thromboprophylaxis after total knee arthroplasty: a randomized comparison. Thromb Res. 2010;126:e298–304.

78. Pendleton RC, Wheeler M, Wanner N, Strong MB, Vinik R, Peters CL. A safe, effective, and easy to use warfarin initiation dosing nomogram for post-joint arthroplasty patients. J Arthroplasty. 2010;25:121–7.

79. Yamaguchi T, Hasegawa M, Niimi R, Sudo A. Incidence and time course of asymptomatic deep vein thrombosis with fondaparinux in patients undergoing total joint arthroplasty. Thromb Res. 2010;126:e323–6.

80. Williams LA, Owen TD. Above-knee versus below-knee stockings in total knee arthroplasty. Ann R Coll Surg Engl. 2006;88:302–5.

81. Niazi AU, Umer M, Umar M. Prophylaxis of DVT with enoxaparin in patients undergoing total knee replacement. J Pak Med Assoc. 2006;56:72–5.

82. Maezawa K, Nozawa M, Aritomi K, Kubota M, Shitoto K, Kurosawa H. Changes of D-dimer after total hip arthroplasty in patients with and without intraoperative heparin. Arch Orthop Trauma Surg. 2008;128:37–40.

83. Pitto RP, Young S. Foot pumps without graduated compression stockings for prevention of deep-vein thrombosis in total joint replacement: efficacy, safety and patient compliance. A comparative, prospective clinical trial. Int Orthop. 2008;32:331–6.

84. Kimura K, Ohtani S, Okamura H, Ishii N, Kishimoto C, Konishi K. Anticoagulation therapy with heparin and warfarin in total knee arthroplasty for osteoarthritis knee. Clin Appl Thromb Hemost. 2009;15:109–12.

85. Elks ML. Conflict of interest and the physician-researcher. J Lab Clin Med. 1995;126:19–23.

86. Economic analysis of health care technology. A report on principles. Task Force on Principles for Economic Analysis of Health Care Technology. Ann Intern Med. 1995;123:61–70.