

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

A Systematic Review

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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 evidence¹⁻³. However, although these evidence-based guidelines or systematic reviews provided high-quality evidence, they could have been affected by the characteristics of the selected studies⁴.

A financial conflict of interest can bias the results of medical or orthopaedic research⁵⁻⁸. 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 funded¹³.

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

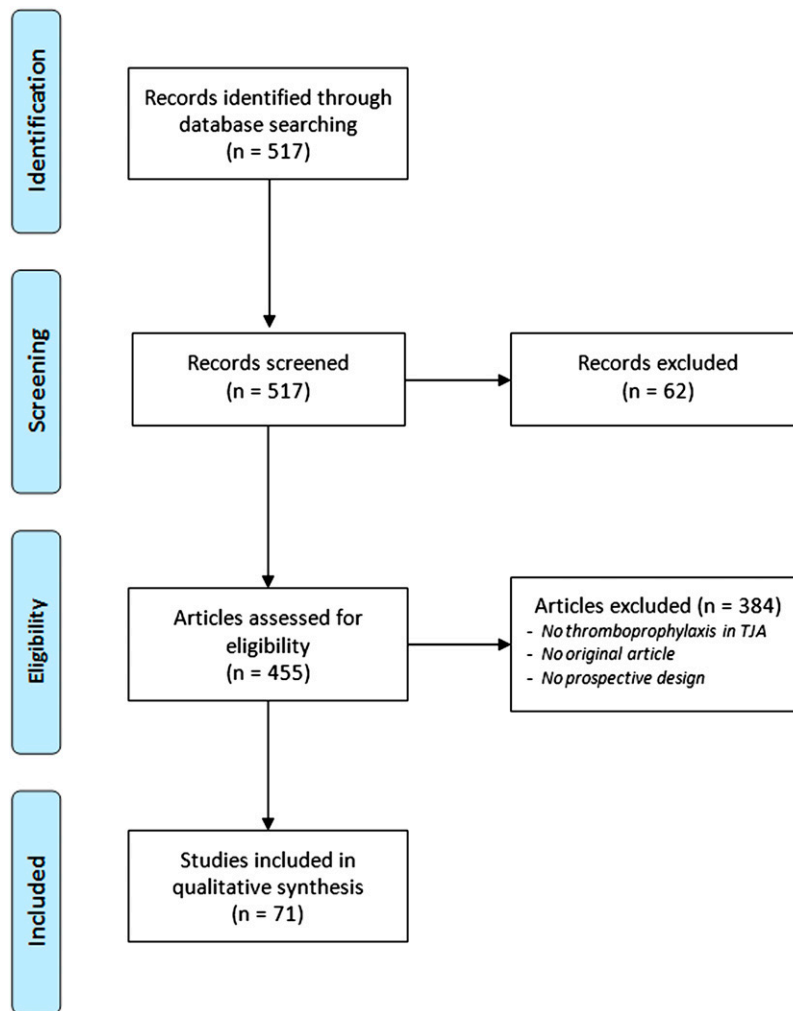


Fig. 1

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 (<i>no. of studies</i>) | | | <0.001 |
| All academic | 18 | 14 | |
| ≥1 company employee | 34 | 0 | |
| Region or country (<i>no. of studies</i>) | | | 0.029 |
| Western | 47 | 9 | |
| Non-Western | 5 | 5 | |
| Department of corresponding author (<i>no. of studies</i>) | | | 0.195 |
| Orthopaedics | 33 | 12 | |
| Nonorthopaedics | 19 | 2 | |
| Design of study (<i>no. of studies</i>) | | | 0.004 |
| With comparator | 46 | 7 | |
| Without comparator | 6 | 7 | |
| Qualitative conclusions (<i>no. of studies</i>) | | | 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 (<i>no. of studies</i>) | | | 0.626 |
| Yes | 37 | 5 | |
| No | 9 | 2 | |
| Statistical test (<i>no. of studies</i>) | | | 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 bias¹⁰⁻¹². Regardless of

the funding source, medical research studies with positive results are published more frequently than those with negative results¹⁰⁻¹². 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 non-inferiority 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 meetings⁸⁵, which can cause unconscious bias in researchers¹².

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 research⁸⁶. 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

 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.

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