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Prevention of Venous Thromboembolism in Major Orthopedic Surgery: Bayesian Network Meta-Analysis of 21 Randomized Trials Evaluating Unfractionated Heparins, Low-Molecular Weight Heparins, and New Oral Anticoagulants

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ABSTRACT

Background: In major orthopedic surgery, prevention of venous thromboembolism has been based on Unfractionated Heparins (UFHs) over the past decades, then on Low-Molecular Weight Heparins (LMWHs), and on New Oral Anticoagulants (NOACs) more recently. To summarize the comparative effectiveness of UFHs, LMWHs, and NOACs in this clinical indication, we applied Bayesian network meta-analysis to the clinical material (randomized studies) published in two previous reviews focused on this issue.
Objectives: Our end-point was a composite of venous thromboembolism and pulmonary embolism.
Materials and Methods: Our analysis was based on standard Bayesian network meta-analysis (random-effect model).
Results: The analysis included 21 randomized trials for a total of 21,805 patients. Our results showed that the degree of effectiveness did not differ among UFHs, LMWHs, and NOACs. Although some trends emerged from an in-depth analysis of these data (e.g. according to the histogram of rankings), no significant differences were found (P > 0.05). Moreover, two agents among LMWHs proved to be adequately supported by randomized trials (enoxaparin and dalteparin), while limited evidence was available for other agents of this class.
Conclusions: Our synthesis of the effectiveness data can be useful as an overall reference in this area and can also contribute to defining the place of further innovative treatments for this clinical indication.

▶ *Implication for health policy/practice/research/medical education:*
   Our synthesis of effectiveness data can be useful for retrospective evaluations in this therapeutic area and also as a reference for defining the place of innovative treatments developed for this clinical indication.

1. Background

For nearly two decades, Low-Molecular Weight Heparins (LMWHs) have been considered as the standard of care for preventing Venous Thromboembolism (VTE) in at-risk patients (1-9). Unfractionated Heparins (UFHs) were the standard of care until the 90s, but then, LMWHs largely imposed themselves for this clinical indication. More recently, Novel Oral Anticoagulants (NOACs) have also been approved for VTE prevention (10), but their use has remained quite limited (e.g. see the annual report on national drug usage issued by the Italian Medicines Agency; report of January to September 2014 at www.agenziafarmaco.gov.it).

2. Objectives

The present study aims to describe an overall analysis of the published clinical trials in which Bayesian network meta-analysis was employed to evaluate the effectiveness of UFHs, LMWHs, and NOACs in preventing VTE in major orthopedic surgery. In doing so, we considered the results of previous meta-analyses. Accordingly, UFHs and

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NOACs were handled as a pooled pharmacological class (as in the previous meta-analysis by Sobieraj et al. (8)), whereas LMWHs were studied by separate evaluation of individual pharmacological agents.

3. Materials and Methods

3.1. Study Design

Our analysis essentially included the following phases: a) definition of the objective of the study (i.e. studying the effectiveness of UFHs, LMWHs, and NOACs in preventing VTE in patients subjected to major orthopedic surgery on the basis of published randomized trials), b) literature search and identification of pertinent studies, c) data extraction according to the pre-planned clinical end-points, and d) statistical comparisons of the effectiveness according to Bayesian network meta-analysis. Since we were aware that some reviews published in the recent years (8, 9) included a very comprehensive literature search, to avoid a hard and unnecessary work, we did not carry out an original literature search and directly relied on the results of the previous authoritative searches.

3.2. Sources of Clinical Material

For selection of the randomized studies included in our analysis, major orthopedic surgery was represented by three types of intervention: Total Hip Arthroplasty (THR), Total Knee Arthroplasty (TKR), and Hip Fracture Surgery (HFS). Additionally, the end-point of our analysis was VTE defined as symptomatic Deep Vein Thrombosis (DVT) or Pulmonary Embolism (PE). The data of the pertinent clinical trials (only randomized studies) were obtained directly from two reviews published between 2012 and 2014 (Sobieraj et al. 2012 (8, 9) and Maratea et al. 2011 (10)). These two previous reviews had in fact the same objective as that of the present study; i.e., evaluation of pharmacological agents for preventing VTE in patients subjected to major surgery. In particular, 13 trials (11) comparing LMWHs and UFHs were drawn from the review by Sobieraj et al. (from Tables 12 and 15 of Sobieraj's article (9)), while 8 trials (11) comparing NOACs and LMWHs were obtained from the meta-analysis performed by Maratea et al. (from the supplementary document of this meta-analysis (10)).

3.3. Outcomes and Data Extraction

The effectiveness data were summarized according to a composite end-point represented by the occurrence of DVT or PE, including fatal cases of PE. The review by Maratea et al. (10) adopted this same composite end-point. However, Sobieraj et al. (9) separately presented the data of symptomatic DVT and PE. Therefore, we recalculated the incidence of the composite end-point by adding the number of PEs to the number of symptomatic DVTs. The raw data of this end-point for the overall series of the included trials have been reported elsewhere (11).

3.4. Design of the Effectiveness Comparisons

To compare various treatments, the class of LMWHs was divided according to the specific agents employed in the trials. Furthermore, enoxaparin was considered as two separate treatments depending on whether this agent was given once daily or twice daily. On the other hand, all NOACs were handled as a single treatment class. This was mainly because the study by Maratea et al. (10) found no significant differences among individual agents. Another reason was that our analysis was mainly focused on LMWHs and, consequently, individual agents were separately considered in the class of LMWHs. Also, all UFHs were kept as a single class to avoid an excessive number of comparators in our Bayesian network meta-analysis (see below).

3.5. Bayesian Network Meta-Analysis

We employed Bayesian network meta-analysis according to the most common model available in this field (12-15). The Bayesian approach to make indirect comparisons is increasingly being used in the recent literature and can be considered the current standard in this field. Compared to the traditional frequentist approach (16), the Bayesian approach has one main advantage in that all treatments included in the comparisons are incorporated into a single model. In contrast, in most frequentist approaches, there are as many separate analyses as the number of comparisons being studied. The output of the network meta-analysis consisted of Odds Ratio (OR) for all combinations of pairwise comparisons. The values of OR were associated with their respective 95% Credible Interval (CrI), reflecting a formal level of statistical significance at 5%. Both direct comparisons and indirect comparisons were considered. It should be noted that the Bayesian model adopted for our analysis (17) (random-effect model and fixed effect model for binary end-points) was developed by the NICE Support Unit, UK (18).

4. Results

Considering the design of our study, the Bayesian analysis was focused on a single clinical end-point; i.e., a composite end-point of DVT and/or PE. In handling the two end-points of DVT and PE, our definition of DVT exactly reflected the one reported by Sobieraj et al. in their review (8, 9). With regards to PE, we employed the information reported in Sobieraj's review, but we extracted the information on this end-point from the full text of individual studies in cases where these data were unavailable from Sobieraj's report (8, 9).

After examining a total of 21 Randomized Controlled Trials (RCTs) (15 for comparison of LMWHs and UFHs and 8 for comparison of NOACs and LMWHs; total number of patients = 21805), the Bayesian network meta-analysis generated the results shown in Figures 1 and 2. The results obtained using the fixed-effect model (data not shown) were associated with a much worse value of goodness-of-fit.

According to Figure 1, all pairwise comparisons showed no significant difference among these active agents. More interestingly, the rankings in effectiveness estimated by the Bayesian probabilistic analysis gave the following results (rankings for individual treatments with 95% CrIs in parenthesis; 1 = the highest effectiveness and 5 = the lowest effectiveness): enoxaparin-bid, 1 (1 to 4); NOACS, 2 (1 to 5); enoxaparin-qd, 3 (2 to 5); UFH, 4 (2 to 5); dalteparin, 5 (1 to 5).

Figure 1. Composite End-Point of Occurrence of DVT or PE
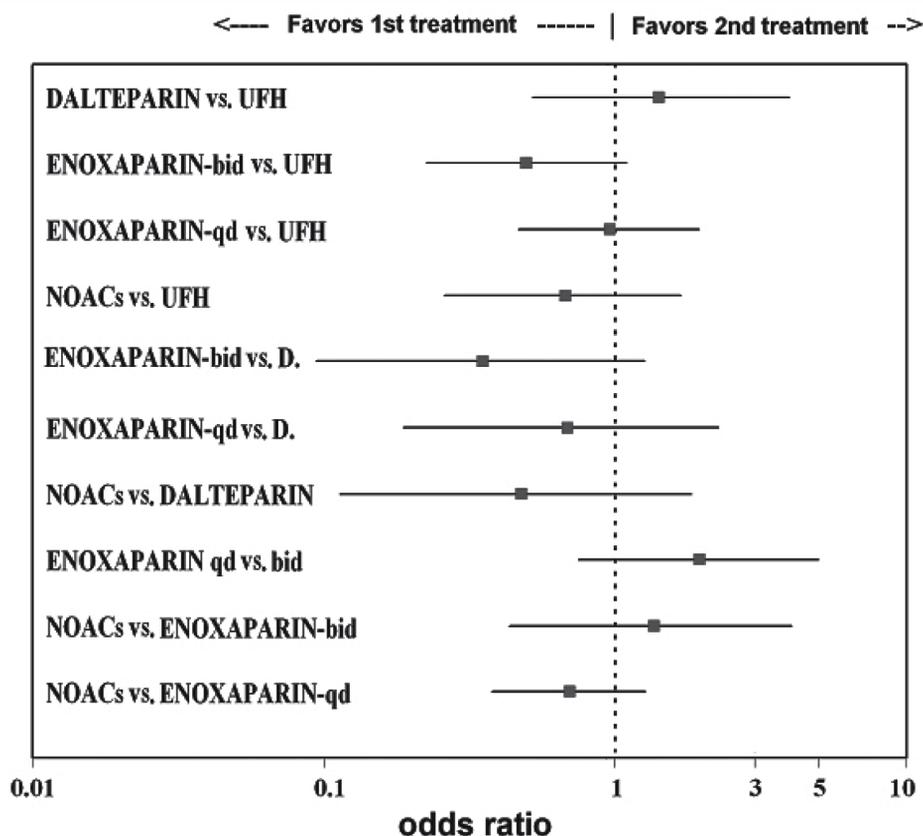
OR values (with 95% CrI) calculated for all direct and indirect comparisons according to the Bayesian random-effect model. The horizontal bars indicate two-sided 95% credible interval for OR of individual comparisons. The numerical values shown in the figure are as follows (95% CrI in parenthesis): dalteparin vs. UFH, 1.41 (0.52 to 3.94); enoxaparin-BID vs. UFH, 0.49 (0.22 to 1.09); enoxaparin-QD vs. UFH, 0.96 (0.47 to 1.93); NOACs vs. UFH, 0.67 (0.26 to 1.67); enoxaparin-BID vs. dalteparin, 0.35 (0.09 to 1.25); enoxaparin-QD vs. dalteparin, 0.68 (0.19 to 2.26); NOACs vs. dalteparin, 0.48 (0.11 to 1.82); enoxaparin-QD vs. BID, 1.95 (0.75 to 4.96); NOACs vs. enoxaparin-BID, 1.36 (0.43 to 4.04); NOACs vs. enoxaparin-QD, 0.70 (0.38 to 1.27).
Abbreviations: QD, once daily; BID, twice daily.

According to these results, enoxaparin twice daily ranked first in effectiveness even though this regimen is not frequently employed in everyday practice. NOACs ranked second, while enoxaparin once daily ranked third. On the other hand, dalteparin had the worst rank. However, as shown in Figure 2, none of the differences among the 5 treatments was statistically significant.

5. Discussion

This article represents the first attempt to conduct an overall evidence-based analysis of the effectiveness of the three main classes of agents indicated in major orthopaedic surgery for the prevention of VTE.

In the first place, since all of the analyses reported in our study were based on a relative outcome measure (i.e, OR) and little information was provided on absolute outcome measures (e.g, the absolute incidence of end-point occurrence), it is worthwhile to consider some information based on absolute incidences. According to the results found in the control groups of the meta-analysis by Sobieraj et al. (8), the event rates (stratified according to the type of surgery, i.e, THR, TKR, and HFS, respectively) were the following: DVT (39% percent, 53% percent, and 47% percent, respectively), PE (6% percent, 1% percent, and

3% percent, respectively), major bleeding (1% percent, 3% percent, and 8% percent, respectively), and minor bleeding (5% percent, 5% percent, and not reported, respectively). These absolute event rates represent a sort of baseline clinical scenario on which the various treatments intervene by exerting their preventive effect. On the one hand, our results suggested a numerical trend, showing an increased effectiveness for more recent agents, such as NOACs and enoxaparin, in comparison to the older ones. On the other hand, our statistical analysis failed to demonstrate any significant difference among the various treatments under examination. Considering our analysis on LMWHs, one interesting finding was the indirect demonstration that enoxaparin had similar effectiveness in comparison with dalteparin (OR for enoxaparin- bid vs. dalteparin: 0.35, 95% CrI: 0.09 - 1.25; OR for enoxaparin-qd vs. dalteparin: 0.68, 95% CrI 0.19- to 2.26). While several guidelines have often mentioned these two LMWHs as the best candidates for patients undergoing major orthopeaedic surgery (19, 20), our analysis is the first that, though indirectly, provided some evidence on whether these two LMWS have similar effectiveness. It should be mentioned that fondaparinux was not included in our study mainly because the sources of clinical data used for our analysis had not studied the role

Figure 2. Histogram of Rankings Generated by the Bayesian Network Meta-Analysis
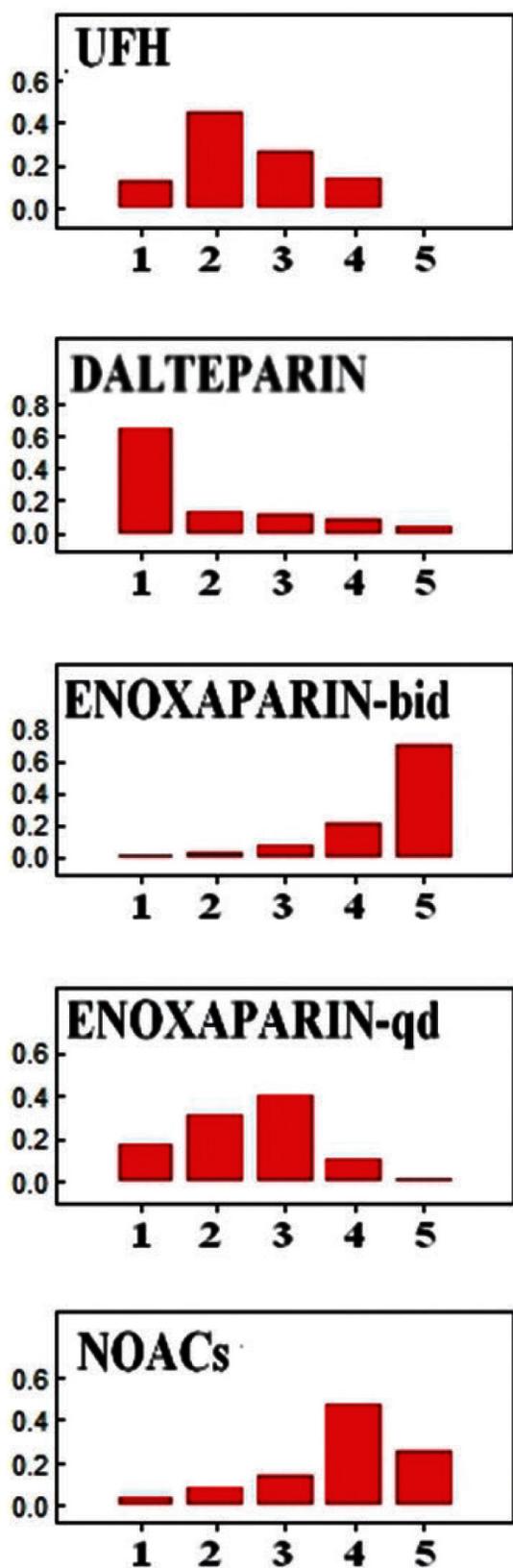
The graphs reflect a total of 20,000 iterations and consist of as many histograms as the treatments included in the analysis (N = 5). In each panel, the histogram shows the percent distribution of the simulations across rank 1 (the least effective treatment) through 5 (the most effective treatment). The y-axis shows probability on a 0 - 1 scale.

of this agent in VTE prevention. One limitation of our study was that our analysis was focused on effectiveness without examining safety. Because of the multiplicity of safety end-points, the likely differences in end-point definitions, and the large number of randomized trials, we thought that a Bayesian analysis on safety was problematic. Hence, the best overview on the safety of these agents remains the study by Sobieraj et al. (9), in which no differences among the different heparins were found concerning the safety end-points (e.g., see Table 13, pg. 215 of the article by Sobieraj et al. (8)). Another limitation of our study was that, despite our choice to study effectiveness and not safety, some heterogeneitiesy on the effectiveness end-points cannot be excluded mainly because the trials covered more than 30 decades and some details on DVT and PE definitions were lacking (particularly in the oldest trials). This is probably the reason why the random-effect model had a better performance in our Bayesian analysis compared to the fixed-effect one. Another limitation was that we did not perform any original literature search, but we directly relied on two previously published studies that had however adopted appropriate methods to identify the clinical material suitable for our analysis.

5.1 Conclusions

The relative efficacy and safety of the LMWHs have never been thoroughly investigated because there are very few direct comparisons among these agents in randomized clinical trials. While recommending among LMWHs for the prevention of VTE, clinical guidelines have not generally specified individual agents. National and international organizations recognize that LMWHs are distinct entities and that they should not be used interchangeably in clinical practice, but comparative data are lacking from clinical guidelines. In this context, the main message conveyed by our analysis is that two LMWHs (enoxaparin and dalteparin) are supported by an adequate evidence for preventing VTE in major orthopedic surgery and show no difference in effectiveness from one another. Nonetheless, other LMWHs that are approved for this clinical indication (nadroparin) do not have the same body of evidence for this indication. On the other hand, the findings of the present study are in keeping with those of a previous evidence-based analysis (7) that was specifically aimed at evaluating the degree of therapeutic equivalence within the class of NOACs.

In conclusion, while the present analysis was simply a re-visitation of a series of previously published information, combining a modern evidence-based technique (Bayesian network meta- analysis) with these datasets allowed us to generate an original "all-in-one" picture of the effectiveness that can be expected from these pharmacological agents for prevention of VTE in major orthopedic surgery. Overall, our synthesis of effectiveness data can be useful for retrospective evaluations in this therapeutic area and also as a reference for defining the place in therapy of innovative treatments developed for this clinical indication (21).

Authors' Contribution

All the 5 authors contributed to a similar extent to the present study. All the 5 authors are independent of any commercial funder. Andrea Messori took responsibility for integrity of the data and accuracy of the data analysis.

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