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LETTER TO THE EDITOR

Letter to the Editor

Potent Anticoagulants Are Associated with a Higher All-cause Mortality Rate After Hip and Knee Arthroplasty

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To the Editor:

The authors of the article "Potent Anticoagulants Are Associated with a Higher All-cause Mortality Rate After Hip and Knee Arthroplasty" published in March 2008 [9] conducted a review of the literature on various thromboprophylactic regimens used for prevention of venous thromboembolism after THA or TKA. Based on an analysis of that review, they concluded so-called "potent" anticoagulants, Group A (low-molecular-weight heparins, ximelagatran, fondaparinux, and rivaroxaban), were associated with higher all-cause mortality than other thromboprophylactic regimens, which were divided into multimodal regimens (Group B) and warfarin (Group C). However, there appear to be serious flaws in the manner in which the data were selected and presented and the methods used for comparison. Therefore, we believe their conclusions are unfounded and require further discussion.

First, the conclusions suggest all "potent" anticoagulants are equivalent, and yet comparative Phase III trials of fondaparinux and rivaroxaban versus enoxaparin show clearly this is not the case [1–3, 6–8, 10]. Furthermore, no rationale is offered for the inclusion in Group A of one drug ximelagatran (Exanta®, AstraZeneca) that was withdrawn because of hepatotoxicity and another drug rivaroxaban (Xarelto®, Bayer HealthCare AG, Wuppertal, Germany) that has not yet received regulatory approval.

Second, there is considerable variability and inconsistency in the quality of data selected for analysis, shown in Table 1. (1) Study populations selected for analysis comprised the safety populations for some studies but the "intention to treat" populations for others. (2) All except one (shown incorrectly) of the Group B studies were nonrandomized. (3) Despite its inclusion in Group A, no data for rivaroxaban are mentioned anywhere in the paper. (4) For the Group A study by Heit et al. [5], the deaths shown include two that occurred while patients were receiving a placebo. (5) Most Group A data presented appear to be for enoxaparin, which therefore cannot be considered representative of all the Group A anticoagulants. (6) Most of the selected studies were not double-blind and did not apply central, blinded adjudication of all outcomes, implying much of the data for pulmonary emboli were based on local reports only. Therefore, any conclusions regarding pulmonary embolism must be considered questionable. (7) With the exception of randomization, Sharrock et al. do not discuss the extent to which the above points might affect the validity of their analysis.

Third, questions must be asked about the methods used for the comparisons between the groups. (1) Mortality and pulmonary embolism rates were not corrected for different

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durations of prophylaxis or observation. Because a substantial proportion of venous thromboembolisms occur after hospital discharge, the absence of any such correction considerably complicates interpretation of the analyses presented in this article. (2) Half (30 of 60) of the Group A deaths occurred in just three of the 12 Group A studies (see Table 1 in Sharrock et al. [9]). Two of these studies completed enrollment by 1996 (see Table 1 in Sharrock et al. [9]) and are unlikely to be representative of modern practice. Similarly, nine of the 14 Group B deaths occurred in just one study (see Table 1 in Sharrock et al. [9]), as did half the warfarin (Group C) deaths. These observations make it unlikely the total number of deaths recorded for each group can be considered representative of the corresponding thromboprophylactic regimen. (3) There is considerable heterogeneity in each group, with mortality rates ranging from 0.00% to 0.62% for Group A, 0.00% to 0.29% for Group B, and 0.10% to 0.67% for Group C. All three of these ranges have considerable overlap. (4) No correction is applied for the use of general versus regional anesthesia, even though the authors point out regional anesthesia was used for 36% of the Group A patients versus 94% of the Group B patients.

Although Sharrock et al. conducted their analysis on the basis of the number of deaths reported for the various studies included, the above points indicate much of the mortality data should either have been corrected for various factors before inclusion in the analysis or should not have been included at all. Without justification for the validity of the included data, it is difficult to conclude an analysis based on those data is valid.

Sharrock et al. [9] include only three studies (see Table 1 in Sharrock et al. [9]) where Group A and Group C regimens are compared within-study. None of the listed studies include a within-study comparison of a Group B regimen with either a Group A or a Group C regimen. Unfortunately, they did not provide full details of the statistical methods used; however, given the relative lack of within-study comparisons, it seems unlikely their methods can provide a valid analysis of treatment comparisons for such heterogeneous study data. Although the authors recognized this limitation, the potential impact of uncontrollable bias in the treatment comparisons is not fully acknowledged. For example, the observed differences could be accounted for by more complete mortality followup in the randomized than in the nonrandomized studies.

The authors note use of regional anesthesia in orthopaedic surgery is associated with a 30% reduction in mortality compared with general anesthesia, although they also argue the differences in the use of regional anesthesia are not sufficient to invalidate their claim for an excess mortality associated with "potent" anticoagulants. However, in light of the above concerns about the quality of the data and the statistical methods used, it seems possible the imbalance in anesthetic protocols between Groups A and B, or other factors such as case volume, could account entirely for the authors' observations.

More importantly, Sharrock et al. [9] do not address the compelling arguments for anticoagulant-based thromboprophylaxis set forth by Geerts et al. [4] in the current American College of Chest Physicians guidelines. These guideline recommendations are evidence-based, and the use of anticoagulant thromboprophylaxis is supported by Grade 1A evidence for THA and TKA. If the authors wished to suggest the most widely used anticoagulant-based thromboprophylaxis protocols are inappropriate, then their arguments would have been considerably strengthened by the inclusion of levels of evidence for their assertions.

We believe this paper suffers from profound defects in data selection and methodology, and as a result, the conclusion that thromboprophylaxis with so-called "potent" anticoagulants is associated with higher all-cause mortality is invalid.

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