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Response to Editorial on CRISTAL VTE trial

Ian Harris
Orthopaedic Surgeon
i. School of Clinical Medicine, UNSW Medicine & Health, South West Sydney Clinical School, Faculty of Medicine and Health, UNSW Sydney, Sydney, NSW, Australia

Other Contributors:

Verinder Sidhu
Orthopaedic Surgeon
i. School of Clinical Medicine, UNSW Medicine & Health, South West Sydney Clinical School, Faculty of Medicine and Health, UNSW Sydney, Sydney, NSW, Australia

Rachelle Buchbinder
Rheumatologist
School of Public Health and Preventive Medicine, Monash University

We thank Parvizi et al for their editorial and interest in our trial. However, we consider most of their concerns to be unfounded. As we were not afforded the opportunity to review their comments prior to publication we appreciate this opportunity to set the record straight.

1. The editorial states that ‘numerous recent randomized studies, have shown that aspirin at a dosage of 81 or 325mg twice per day, is an effective and safe modality for VTE prophylaxis in patients undergoing TJA.’ To the contrary, no adequately powered randomized study has demonstrated this to be true for aspirin monotherapy for symptomatic VTE prophylaxis. Of the six studies referenced to support this statement, two used an alternate form of prophylaxis prior to randomization to extended prophylaxis with aspirin (1, 2). However the results from CRISTAL (figure 3) demonstrated the VTE rate was highest within the first 10 days after surgery and the safety of aspirin monotherapy cannot be supported from these two studies. Another two studies were underpowered, only including 70 (3) and 275 (4) patients, respectively. The fifth study was a meta-analysis of randomized trials that grouped together studies including asymptomatic and symptomatic VTE (5). Screening for asymptomatic VTE is no longer recommended or performed (6, 7). The final study, the Pulmonary Embolism Prevention (PEP) trial commenced patient recruitment 30 years ago (1992), compared aspirin to placebo (not other VTE prophylaxis agents) and focused primarily on hip fracture patients (elective arthroplasty only represented 23% of included patients) (8). It therefore provides no information about the effectiveness of aspirin compared to current alternatives.

2. In response to the concern raised about the dose of aspirin we used, aspirin doses of 30 to 100mg daily are sufficient to inhibit platelet thromboxane-A2 (9) and doses ranging from 81mg to 162mg are effective for thrombosis prevention (1, 10, 11). The most recent Canadian trial used a dose of 81mg daily,(1) which was also within the dose range (75-150mg) recommended by the most recent VTE prophylaxis guidelines published in the United Kingdom (12). Aspirin is available at 100mg or 300mg in Australia, and the use of 100mg daily was considered appropriate for this study.

The use of 81mg twice daily does not reflect the dosage of aspirin used in Canada, the United Kingdom or Australia. The PEP trial was again cited to support their concern, however the intervention tested in this trial no longer reflects modern-day practice, let alone elective arthroplasty practice.

3. In response to the concern that some patients in the enoxaparin group were treated with “dual” prophylaxis (received single antiplatelet therapy and enoxaparin), our subgroup analyses (Figure 2) demonstrated consistent results, with or without preoperative single antiplatelet use. Similar to the study published by Anderson et al (1), the primary outcome was not affected by long-term preoperative single antiplatelet therapy.

4. The authors note that the symptomatic 90-day VTE rates for patients with a prior VTE were 8.5% and 2.6%, in the aspirin and enoxaparin groups respectively. This shows that aspirin is less effective than enoxaparin in this subgroup. We think that Parvizi et al may be suggesting that past history of VTE was imbalanced between the groups, or that the inferiority of aspirin was isolated to this sub-group. However, the rates of prior VTE for the aspirin and enoxaparin groups were 5.2% and 6.3% respectively, showing good balance, and the subgroup analysis showed that aspirin was significantly inferior to enoxaparin for both those with a past history of VTE and those without a past history of VTE.

5. The concern that we failed to report on some other important parameters such as the rate of wound-related complications is easily refuted. The secondary outcome of joint-related reoperation (at 90-days and 6 months) included re-operation for wound complications such as dehiscence, haematoma and deep joint infection. There were no between-group differences in this outcome at any time point. A manuscript reporting the results of a sub-study comparing wound drainage rates between prophylaxis groups which supports these findings is currently in preparation.

6. Parvizi et al and Bhandari et al (13) have suggested that enoxaparin use may be associated with increased secondary complications such as bleeding. However, there was no increased risk of secondary complications (death, reoperation, readmission, major bleeding) with enoxaparin use in our trial or with rivaroxaban use in the trial by Anderson et al (1).

Finally, while we are encouraged by the attention given to our trial, we are concerned about the attempts to discredit the study despite it being the first adequately powered study to provide causal evidence linking higher VTE rates to aspirin compared to enoxaparin, and by the preferred acceptance of observational evidence over experimental evidence, apparently based on supporting prior beliefs. Indeed, the purported benefits of aspirin as stated in the editorial (on mortality, infection, stiffness, readmission, reoperation and wound-related complications) are all based upon observational studies. Rather than discussing the limitations of these studies, the authors incorrectly conclude a causal association by stating that aspirin “led to” these benefits. The arguments against randomized trials are largely addressed by this causal study, which was large scale, embedded in routine practice, audited, registered a priori, and used a published protocol and statistical analysis plan, blinded analysis and blinded manuscript preparation. We ask the editorial authors and readers to consider whether our trial would have received such negative scrutiny if it had shown twice the rate of VTE in the enoxaparin group instead of the aspirin group.

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Conflict of Interest: None Declared