We welcome letters to the Editor concerning articles which have recently been published. Such letters will be subject to the usual stages of selection and editing; where appropriate the authors of the original article will be offered the opportunity to reply.

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Oral rivaroxaban for the prevention of symptomatic venous thromboembolism after elective hip and knee replacement

Sir,

We read with interest the papers by Eriksson et al¹ and by Cusick and Beverland² in the May 2009 issue, entitled "Oral rivaroxaban for the prevention of symptomatic venous thromboembolism after elective hip and knee replacement" and "The incidence of fatal pulmonary embolism after primary hip and knee replacement in a consecutive series of 4253 patients", respectively. In their study - funded by the manufacturers of rivaroxaban - Eriksson et al,¹ report a lower thromboembolic "event rate" with rivaroxaban than with enoxaparin. Their endpoint is a composite measure of thromboembolism and all-cause mortality. This measure is a surrogate endpoint and they do not report the data for rates of fatal pulmonary embolism, which is arguably the only important endpoint when studying venous thromboembolism.

It is also interesting to note the significantly different age profiles in the two studies, which look at different populations. This underlines the problem of the difference between efficacy - results in a controlled, limited, select but randomised, population- and effect - namely their translation into the general population. This was the subject of review by the NHS Health Technology Assessment report (HTA),³ which counsels against the use of such surrogate endpoints, stating that "reliance on surrogate outcomes can ultimately lead to harmful patient outcomes".

Cusick and Beverland² report a rate of fatal pulmonary embolism of only three in 4253 (0.07%) cases of hip or knee arthroplasty. This rate is very similar to the rate of fatal pulmonary embolism of 0.06% observed in a series of 5100 total knee arthroplasty cases from our unit.⁴ Taking together these two independent, unfunded studies using hard clinical endpoints, we agree with the conclusion of Cusick and Beverland² that, in patients without additional risk factors, arthroplasty surgery is not a high-risk procedure for fatal pulmonary embolism.

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Author's reply:

Sir,

We thank Messrs Clayton et al for their interest in our paper. However, we have to correct a misinterpretation of our study: surrogate endpoints were not used in this analysis; only pre-specified symptomatic endpoints were included. The large patient numbers in our database allowed an analysis of the composite endpoint of symptomatic venous thromboembolism (VTE) and all-cause mortality.

The clinical importance of symptomatic VTE complications should not be underestimated in terms of patient burden, economic cost and quality of life. Focusing on fatal pulmonary embolism only, as noted in the letter by Clayton et al, is scientifically and medically inaccurate.

From a clinical perspective, symptomatic VTE can lead to prolonged hospitalisation, increased NHS costs and long-term sequelae such as recurrent VTE, post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension, which can affect morbidity, mortality and quality of life.^{1,2} Moreover, fatal pulmonary embolism is now a rare event in this population and, as Clayton et al discuss in their paper, clinical studies enrolling very large patient numbers would be required to demonstrate a significant reduction in fatal pulmonary embolism.³ The incidence of fatal pulmonary embolism is reported in our paper (0% with rivaroxaban, < 0.01% with enoxaparin regimens). However, as clinicians are well aware, the reported incidence of fatal pulmonary embolism is not always accurate given the very low autopsy rate.

Despite the differences noted in age profiles between our study and that of Cusick and Beverland,⁴ the patient demographics in the RECORD 1-3 analysis were representative of those seen in clinical practice, as supported by demographic data from the GLORY registry.⁵ Importantly, in our study there was no upper age limit, no weight limit and, although not a predominant subgroup, patients undergoing revision surgery were included.

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