Rivaroxaban for the prevention of venous thromboembolism: a single technology appraisal

M Stevenson,* A Scope, M Holmes, A Rees and E Kaltenthaler

School of Health and Related Research (ScHARR), University of Sheffield, UK

*Corresponding author

Declared competing interests of authors: none

Abstract

This paper presents a summary of the evidence review group (ERG) report into the clinical effectiveness and cost-effectiveness of rivaroxaban for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery based upon a review of the manufacturer's submission to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. The submission's evidence came from four randomised controlled trials (RCTs) comparing rivaroxaban with enoxaparin [RECORD (Regulation of Coagulation in Orthopedic surgery to pRevent Deep venous thrombosis and pulmonary embolism) 1–4] and three comparing dabigatran with enoxaparin [RE-NOVATE (the prevention of venous thromboembolism after total hip replacement trial), RE-MODEL (the prevention of venous thromboembolism after total knee replacement trial) and RE-MOBILIZE (the prevention of venous thromboembolism after total knee arthroplasty trial)]. The evidence from the four RECORD trials indicates that rivaroxaban had superior efficacy over enoxaparin after total hip replacement (THR) and total knee replacement (TKR). For the composite primary outcome of any deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE) and death from all causes the relative risk reductions were 70–79% in THR and 31–49% in TKR. Rivaroxaban also had superior efficacy over enoxaparin for the secondary outcome major VTE. Rivaroxaban was not inferior to enoxaparin on the safety outcome of major bleeding. After the correction of some errors found by the ERG, the manufacturer's economic model represented a reasonable model

HTA 08/03/01

Date of ERG submission:
13 March 2009

TAR Centre(s):
School of Health and Related Research (ScHARR)

List of authors:
M Stevenson, A Scope, M Holmes, A Rees and E Kaltenthaler

Contact details:
Matt Stevenson, School of Health and Related Research (ScHARR), 30 Regent Street, University of Sheffield, Sheffield S1 4DA, UK

E-mail: m.d.stevenson@shef.ac.uk

The research reported in this article of the journal supplement was commissioned and funded by the HTA programme on behalf of NICE as project number 08/03/01. The assessment report began editorial review in February 2009 and was accepted for publication in April 2009. See the HTA programme website for further project information (www.hta.ac.uk). This summary of the ERG report was compiled after the Appraisal Committee's review.

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Discussion of ERG reports is invited. Visit the HTA website correspondence forum (www.hta.ac.uk/correspond).

of patients receiving prophylaxis for THR or TKR. In the base-case analyses rivaroxaban dominated both enoxaparin and dabigatran. The incremental costs saved and quality-adjusted life-years (QALYs) gained were small (below £200 and 0.005, respectively, per person). Analyses were conducted sampling from the distributions observed from the RCTs. When all parameters were sampled rivaroxaban dominated enoxaparin in all scenarios except for two, in which enoxaparin produced more QALYs than rivaroxaban and had an incremental cost per QALY gained of £5000 and £8000 respectively. Rivaroxaban dominated dabigatran when RECORD 1 and RECORD 2, individually or pooled, were compared with RE-NOVATE and when all four rivaroxaban RCTs pooled were compared with all three dabigatran RCTs. Dabigatran dominated rivaroxaban comparing RECORD 4 with RE-MODEL and RE-MOBILIZE, and was more cost-effective than rivaroxaban comparing RECORD 3 (incremental cost per QALY gained of rivaroxaban compared with dabigatran of £123,000) or RECORD 3 and RECORD 4 pooled (incremental cost per QALY gained of dabigatran compared with rivaroxaban of £400) with RE-MODEL and RE-MOBILIZE. In conclusion, the evidence indicates that rivaroxaban is not inferior to enoxaparin in terms of the primary and secondary outcomes. The submission presents a reasonable estimation of the cost-effectiveness of rivaroxaban compared with enoxaparin and dabigatran, although the uncertainty in the decision has been underestimated. The results are particularly sensitive to any assumed difference in the number of fatal PEs, but the ERG does not believe there is sufficient evidence to support a difference between interventions. The NICE guidance issued as a result of the STA states that: riveroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective THR or elective TKB.

Introduction

The National Institute of Health and Clinical Excellence (NICE) is an independent organisation within the NHS that is responsible for providing national guidance on the treatment and care of people using the NHS in England and Wales. One of the responsibilities of NICE is to provide guidance to the NHS on the use of selected new and established health technologies, based on an appraisal of those technologies.

NICE's single technology appraisal (STA) process is specifically designed for the appraisal of a single product, device or other technology, with a single indication, for which most of the relevant evidence lies with one manufacturer or sponsor.[1] Typically, it is used for new pharmaceutical products close to launch. The principal evidence for an STA is derived from a submission by the manufacturer/sponsor of the technology. In addition, a report reviewing the evidence submission is submitted by the evidence review group (ERG), an external organisation independent of NICE. This paper presents a summary of the ERG report for the STA of rivaroxaban for the prevention of venous thromboembolism (VTE),[2] which followed a manufacturer's submission by Bayer Schering Pharma.[3]

Description of the underlying health problem

The manufacturer's submission reported that there are approximately 25,000 deaths each year in England due to VTE. This figure includes not only those undergoing surgery but also those admitted to hospital for the medical care of serious illnesses and will overestimate deaths associated with total hip and knee replacement.[3]

Scope of the ERG report

The manufacturer's submission reported on the clinical and cost-effectiveness of rivaroxaban (Xarelto®) for the prevention of VTE in adult patients undergoing elective hip or knee replacement surgery. The recommended dose of rivaroxaban is 10 mg taken orally once daily. The duration of treatment recommended in the summary of product characteristics depends on the type of orthopaedic surgery. Patients undergoing total hip replacement (THR) have a recommended treatment duration of 5 weeks; this value is 2 weeks for total knee replacement (TKR). The acquisition cost of rivaroxaban reported in the manufacturer's submission was £4.50 per day.

The manufacturer's submission considered enoxaparin, a low-molecular-weight heparin (LMWH), as the most relevant comparator, as reflected in the scope. A weighted comparison against all LMWHs was presented as a sensitivity analysis assuming equal efficacy between all LMWHs. Indirect comparisons with dabigatran

(which NICE has recommended as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective THR or elective TKR[4]) were undertaken. The majority of outcome measures identified in the scope [mortality, incidence of symptomatic and asymptomatic VTE, pulmonary embolism (PE)], and safety outcomes (bleeding events), were reported. However, outcomes relating to knee and hip joints, although identified in the scope, were not reported.

Clinical data on effectiveness were taken from four randomised controlled trials (RCTs) of rivaroxaban compared with enoxaparin [RECORD (Regulation of Coagulation in Orthopedic surgery to pRevent Deep venous thrombosis and pulmonary embolism) 1–4[5–8]] and from three RCTs of dabigatran compared with enoxaparin [RE-NOVATE (the prevention of venous thromboembolism after total hip replacement trial),[9] RE-MODEL(the prevention of venous thromboembolism after total knee replacement trial)[10] and RE-MOBILIZE (the prevention of venous thromboembolism after total knee arthroplasty trial)[11]].

The manufacturer submitted a model in Microsoft EXCEL. The model was divided into a prophylaxis stage (a period of 35 days for THR and 12 days for TKR), a postprophylaxis stage (until 3 months after surgery) and a long-term complication stage (assumed to end when a patient died or became 101 years of age). The initial two stages were assessed using a decision trees, whereas the third phase was divided into a 5-year period, in which VTE, post-thrombotic syndrome (PTS) or death could occur, followed by a duration in which only transitions to death were allowed. The base case in the manufacturer's submission assumed that only those parameters that were statistically significantly different would be varied between rivaroxaban and the comparator. Additional analyses requested by the ERG used all variables regardless of statistical significance.

Methods

The ERG report comprised a critical review of the evidence for the clinical effectiveness and cost-effectiveness of the technology based upon the manufacturer's/sponsor's submission to NICE as part of the STA process.

The searches performed by the manufacturer were examined by the ERG and found to be satisfactory. Repeat searches were performed by the ERG and no additional relevant trials were identified. The ERG is confident that all relevant studies were included in the manufacturer's submission and details of ongoing trials that are likely to be reporting additional evidence within 12 months were reported. The inclusion/exclusion criteria appeared to be appropriate; they included appropriate detail and a rationale for the inclusion and exclusion criteria was provided. The reasons provided for excluding studies were all justified.

The manufacturer's submission reported on efforts to ensure blinding but did not report if any of these studies assessed the success of blinding, as required by point 11 on the Consolodated Standards of Reporting Trials (CONSORT) checklist (www.consort-statement.org/). The view of the ERG is that such assessments were not undertaken.

The manufacturer's submission answered the questions suggested by NICE for validity assessment. The ERG assessed the validity of the three published trials (RECORD 1, RECORD 2 and RECORD 3) and the trial information for RECORD 4. This was found to be satisfactory and of adequate methodological quality.

The manufacturer's submission used the modified intention-to-treat (MITT) population in the analyses of the trials. The MITT population was defined as the number of patients who were: (1) valid for safety analysis; (2) had the appropriate surgery; and (3) had an adequate assessment of thromboembolism. The ERG judged this to be an appropriate approach.

The manufacturer's submission contained a series of meta-analyses. Each comparison was conducted initially using a fixed-effects model, with a random-effects model performed if heterogeneity was observed between studies. Theoretically this approach is incorrect as a decision on the most appropriate model should be made before analysis, but this methodology did not materially affect the conclusions.

The deterministic results produced by the model matched those reported in the manufacturer's submission. The results from probabilistic sensitivity analyses were not checked because the ERG found errors within the model. These errors were identified by a thorough, although not exhaustive, review of the model structure and internal logic and the responsiveness of the results to changes in parameter values.

Results

Summary of submitted clinical evidence

In RECORD 1, 3 and 4, rivaroxaban was demonstrated to have superior efficacy over enoxaparin after THR and TKR. RECORD 2 also demonstrated superiority comparing 35 days of rivaroxaban with 12–14 days of enoxaparin. Based on the composite primary end point of any deep vein thrombosis (DVT), non-fatal PE and death from all causes the relative risk reductions were 70–79% in THR and 31–49% in TKR. Rivaroxaban was also demonstrated to have superior efficacy over enoxaparin in RECORD 1, 2 and 3 for the secondary end point of major VTE. Superior efficacy was also shown for the symptomatic VTE end point in RECORD 2 and RECORD 3.

There were no adverse events that were significantly different between rivaroxaban and enoxaparin. Major bleeding occurred more frequently in patients on rivaroxaban. Individually there was no statistically significant difference in major bleed rates between patients receiving rivaroxaban and those receiving enoxaparin, although all point estimates favoured enoxaparin treatment. On meta-analysing all four RCTs, the results remained non-significant in a fixed-effects model ($p = 0.697$). The point estimate favoured enoxaparin rather than rivaroxaban (relative risk 1.8516, 95% CI 0.9434 to 3.6340). Clinical evidence, where not commercial-in-confidence, is presented in Chapter 6 of the manufacturer's submission.

The indirect comparison with dabigatran was marked as commercial-in-confidence in the manufacturer's submission.

Summary of submitted cost-effectiveness evidence

In the base-case analyses rivaroxaban was shown to dominate [i.e. produce more quality-adjusted life-years (QALYs) at a lower cost] both enoxaparin and dabigatran. The incremental costs saved and QALYs gained were small (typically below £200 and 0.005, respectively, per person).

Analyses were conducted sampling from the distributions observed from the RCTs (or indirect comparison with dabigatran) regardless of statistical significance. These results were firmly driven by the assumed impact on fatal PE. Unfortunately this parameter was excluded within the probabilistic sensitivity analyses, which rendered the uncertainty generated in the remaining parameters as largely redundant. Using RECORD 4 alone, enoxaparin produced more QALYs than rivaroxaban and had an incremental cost per QALY gained of approximately £5000; using the pooled results this value was approximately £8000. These results imply that enoxaparin was more cost-effective than rivaroxaban in both of these scenarios using current recommended thresholds.[12]

When dabigatran was used as the comparator, rivaroxaban dominated dabigatran when RECORD 1 individually, RECORD 2 individually or the pooled results from RECORD 1 and RECORD 2 were compared with RENOVATE and when all four rivaroxaban RCTs pooled were compared with all three dabigatran RCTs. Dabigatran dominated rivaroxaban using RECORD 4 compared with RE-MODEL and RE-MOBILIZE, and was more cost-effective than rivaroxaban using RECORD 3 compared with RE-MODEL and RE-MOBILIZE (an incremental cost per QALY gained of rivaroxaban compared with dabigatran of approximately £123,000) and when RECORD 3 and RECORD 4 were pooled and compared with RE-MODEL and RE-MOBILIZE (an incremental cost per QALY gained of dabigatran compared with rivaroxaban of approximately £400).

Commentary on the robustness of submitted evidence

Appropriate analyses and comparisons were included in the manufacturer's submission. Data on the final primary outcome measure (all-cause mortality) were not presented or meta-analysed. The ERG have inferred that this was due to no additional deaths bar fatal PE, the data for which were presented as commercial-in-confidence. The ERG has no concerns with the methodology used for the evidence syntheses. The reporting and interpretation of the safety data were good.

Following dialogue iterations with the ERG team, the resultant EXCEL file was a reasonable model of patients receiving prophylaxis for THR or TKR. The iterations were needed to amend errors found by the ERG, which included incorrect use of standard errors, probabilities becoming negative and some cells being incorrectly cleared.

The probabilistic sensitivity analyses did not capture all of the uncertainty present within the decision. The number of total VTEs for rivaroxaban is assumed to equal the rates observed

in the appropriate RCT(s). For both rivaroxaban and the comparator the proportions of total VTEs that are symptomatic, non-fatal and fatal are fixed at the rates observed in the appropriate RCTs. These are relatively small numbers. For example, in RECORD 1 there were 18 VTEs of which four were non-fatal PE; fixing the proportion of non-fatal PEs to 0.22 (4/18) of the total VTEs will result in considerable uncertainty being excluded compared with a more appropriate approach of sampling this value from a beta distribution. The long-term effects of major bleeding, in particular those that are intracranial, were excluded from the model, although the manufacturer subsequently conducted an external calculation which showed that this omission did not markedly affect the results for the comparison with enoxaparin. The ERG conducted a similar calculation for the comparison with dabigatran, with similar conclusions.

Following the postprophylaxis stage of the model all VTE events are assumed to be DVT. This is conservative and will be unfavourable to the intervention that has the lowest number of VTEs, which is generally rivaroxaban.

The utility of a patient was set to that of a 50-year-old and does not decline as the simulated patient ages. This will favour the intervention that has the greater estimated number of patients alive following the postprophylaxis stage. The manufacturer conducted additional analyses to assess the impact of altering the underlying utility, with only a minor reduction in the incremental QALYs gained associated with rivaroxaban. The manufacturer concluded that the inaccuracy introduced by not altering the utility will be small. The ERG agrees with this conclusion.

Conclusions

The manufacturer's search strategy was adequately reported and the submission appears to contain all of the relevant head-to-head RCTs. The outcomes selected were relevant and appropriate, although joint outcomes, included in the final scope issued by NICE, were excluded as none of the trials reported this.

Processes and validation of study screening and data extraction appear to be appropriate. Statistical methods were explicitly described for the meta-analyses and indirect comparisons and all relevant analyses were performed, although reporting of the results of these analyses were limited because of the omission of conclusions or plots to aid interpretation. The manufacturer's submission appears to contain an unbiased estimate of the treatment effect of rivaroxaban in relation to the relevant outcomes and the comparator enoxaparin. Overall the evidence from the four RECORD trials in the manufacturer's submission indicates that rivaroxaban 10 mg once daily is not inferior to the comparator enoxaparin in terms of the total VTE and all-cause mortality, symptomatic VTE, non-fatal PE and fatal PE. Rivaroxaban was also indicated not to be inferior to the comparator on the safety outcome of major bleeding.

The ERG believes that, following iterations with the ERG, the manufacturer's submission represents a reasonable estimation of the cost-effectiveness of rivaroxaban compared with enoxaparin and dabigatran, although the uncertainty in the decision has been underestimated. This is important as the costs and QALYs accrued by all interventions were similar and the incremental differences reported were small, typically below £200 and 0.005, respectively, per person.

The ERG notes that the results are particularly sensitive to any assumed difference in the number of fatal PEs, but does not believe that there is sufficient evidence to support a difference between interventions.

Summary of NICE guidance issued as a result of the STA

The guidance states that:

Rivaroxaban, within its marketing authorisation, is recommended as an option for the prevention of venous thromboembolism in adults having elective THR or elective TKB.

Key references

1. National Institute for Health and Clinical Excellence. *Guide to the single technology (STA) process*. 19 September 2006. URL: www.nice.org.uk/page.aspx?o=STAprocessguide.

2. Stevenson M, Scope A, Holmes M, Rees A, Kaltenthaler E. *Rivoroxaban for the treatment of venous thromboembolism: a single technology appraisal*. URL: www.ncchta.org/project/1773.asp?SearchText=erglisting.

3. Bayer Healthcare, Bayer Schering Pharma. *Single technology appraisal (STA) of rivaroxaban (Xarelto) for the prevention of venous thromboemobolism (VTE) in adult patients undergoing elective hip or knee replacement surgery*. Manufacturer submission to NICE; 2008.

4. *Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults: a single technology appraisal*. URL: www.nice.org.uk/nicemedia/pdf/TA157Guidance.pdf.

5. Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008;**358**:2765–75.

6. Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboemolism after total hip arthroplasty. *Lancet* 2008;**372**:31–9.

7. Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 2008;**358**:2776–86.

8. Bayer Healthcare. *Pharmaceutical amendment A to RECORD 4 study: REgulation of Coagulation in ORthopedic surgery to prevent DVT and PE: a controlled, double-blind, randomised study of BAY 59–7939 (rivaroxaban) in the prevention of VTE in subjects undergoing elective total knee replacement*. Study number 11355. Report No. MRR A41857; 2008.

9. Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, *et al*.; RE-NOVATE study group. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet* 2007;**370**:949–56.

10. Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost* 2007;**5**:2178–85.

11. Ginsberg JS, Davidson BL, Comp PC, Francis CW, Friedman RJ, Huo MH. The RE-MOBILIZE Writing Committee. The oral inhibitor dabigatran etexilate vs the North American enoxaparin regimen for the prevention of venous thromboembolism after knee arthroplasty surgery. *J Arthroplasty* 2009; in press.

12. National Institute for Health and Clinical Excellence. *Guide to the methods of technology appraisal*. June 2008. URL: www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf.