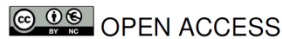


RESEARCH

Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons



OPEN ACCESS

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Introduction

Venous thromboembolism, which encompasses deep vein thrombosis and pulmonary embolism, is responsible for the death of more than half a million people in Europe each year and is the third leading cause of death from cardiovascular causes only ahead of myocardial infarction and stroke.² Additionally, 1.66 million cases of non-fatal symptomatic venous thromboembolism are diagnosed in Europe each year, with two thirds being acquired in hospital.¹ Venous thromboembolism represents an important problem in patients admitted to hospital, including those undergoing major orthopaedic surgery.^{3 4}

The therapeutic arsenal of anticoagulants available for prophylaxis against venous thromboembolism is mainly composed of parenteral agents, such as low molecular weight heparins or fondaparinux.³ These agents are effective and safe but require daily subcutaneous injections, which may be problematic in some patients. Dabigatran etexilate (Pradaxa; Boehringer Ingelheim International, Germany),⁵ rivaroxaban

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Search strategy
Results of secondary efficacy outcomes
Results of secondary safety outcomes
Sensitivity analyses of direct comparisons
Sensitivity analyses of indirect comparisons
Funnel plots

(Xarelto; Bayer Pharma, Germany),⁶ and apixaban (Eliquis; Bristol-Myers Squibb/Pfizer EEIG, United Kingdom),⁷ are new oral anticoagulants available for prophylaxis against venous thromboembolism in patients undergoing total hip or knee replacement surgery. The pivotal studies on these indications are mainly based on findings from mandatory venography of the legs, which is not routinely carried out in standard practice. Definitions for bleeding may differ between studies, however, leading to an underestimation of bleeding risk in some cases.⁸⁻¹⁰ Therefore the effect of the new oral anticoagulants on clinical outcomes is uncertain. In addition, no up to date head to head comparisons have been done between these new oral anticoagulants.

We systematically reviewed and meta-analysed data from randomised controlled trials of the new oral anticoagulants for prophylaxis against venous thromboembolism in patients undergoing total hip or knee replacement. We made direct comparisons with enoxaparin and indirect comparisons between the new oral anticoagulants on the clinical outcomes of symptomatic venous thromboembolism, bleeding, and death.

Methods

We considered randomised controlled trials comparing any of the approved new oral anticoagulants (rivaroxaban, dabigatran, and apixaban) with enoxaparin in patients undergoing total hip or knee replacement. At least one of the daily doses tested in the experimental arms had to correspond to the total daily dose approved for the new oral anticoagulant (dabigatran 220 mg or 150 mg, apixaban 5 mg, or rivaroxaban 10 mg). At least one of the daily doses tested in the control groups had to correspond to the approved regimens for enoxaparin: 40 mg once daily started 12 hours before surgery (Europe) or 30 mg twice daily started 12-24 hours after surgery (North America).

Trial identification and data collection

We searched Medline and CENTRAL (up to April 2011), clinical trial registries, relevant conference proceedings, and websites of regulatory agencies (see supplementary file for search strategy). No language restrictions were applied. Two investigators (AG-O and AIT-F) independently and separately assessed trials for eligibility and extracted data. If a trial was covered in more than one report we used a hierarchy of data sources: public reports from regulatory authorities (US Food and Drug Administration, European Medicines Agency), peer reviewed articles, reports from the web based repository for results of clinical studies, and other sources. Finally, we contacted sponsors or the main investigators for missing outcome data.

Study characteristics and quality

To assess whether the trials were sufficiently homogeneous to be meta-analysed we collected data on patients' characteristics (age and sex), percentage of patients evaluable for efficacy and safety, dosage used in the experimental and control groups, duration of treatment and follow-up, inclusion and exclusion criteria, definitions of outcomes, adjudication committees of venographies and clinical events, type of surgery (total hip or knee replacement), and rate of events in the enoxaparin control group. Additionally, we assessed study quality using the Jadad scale.¹¹

Outcome measures

The prespecified primary outcome was symptomatic venous thromboembolism—that is, symptomatic deep vein thrombosis or symptomatic pulmonary embolism. The prespecified primary safety outcome was clinically relevant bleeding—that is, major bleeding or clinically relevant non-major bleeding. The main secondary outcomes were each of the components of the primary efficacy and safety outcomes, as well as all cause death and a net clinical outcome of hard endpoints, defined as the composite of symptomatic venous thromboembolism, major bleeding, and all cause death.

Statistical analysis

We carried out direct comparisons between dabigatran, rivaroxaban, and apixaban versus enoxaparin as well as indirect comparisons between the three drugs on an intention to treat basis, according to PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) recommendations.¹²

For the meta-analysis we calculated relative risks and their respective 95% confidence intervals for each study and for the pooled studies for each of the anticoagulants. Heterogeneity was assessed using the Cochran Q test¹³ and the Higgins I² test.¹⁴ A Cochran's Q P<0.10 and I²>50% were considered to show significant heterogeneity.¹⁴ We used the random effects model described by Der-Simonian and Laird for the main analysis.¹⁵ We carried out subgroup analyses of trials with the different anticoagulants as well as in hip and knee replacement. P<0.05 for interaction indicates that the effect of treatment differs between the tested subgroups. As a sensitivity analysis, we calculated the results using the fixed effects method described by Mantel and Haenszel.¹⁶ Additional sensitivity analyses were done taking into account certain methodological problems that could influence the results of the meta-analysis: study phase, study quality, and duration of thromboprophylaxis. We created funnel plots showing the standard error and the effect size to evaluate publication bias. Direct comparisons were done using the RevMan statistical software, version 5.1 (Nordic Cochrane Center).¹⁷ For indirect comparisons (Bucher's method), we used the ITC (Indirect Treatment Comparison) computer program, version 1.0.¹⁸

Results

The literature search identified 606 articles, 71 of which related to clinical trials or protocols with rivaroxaban, dabigatran, or apixaban (fig 1). Of these, 19 were clinical trials in total hip or knee replacement¹⁹⁻³⁷ and were selected for checking as full text. Sixteen of the studies were eligible for inclusion¹⁹⁻³⁴ and the remaining three,³⁵⁻³⁷ all with dabigatran, were excluded because they did not include a control group,³⁵ did not include a dabigatran 150 mg or 220 mg daily dose group,³⁶ or used placebo as control rather than enoxaparin.³⁷

Table 1 shows the characteristics of the trials and treatments. The 16 studies comprised 38 747 patients and compared dabigatran (four studies),¹⁹⁻²² rivaroxaban (eight studies),²³⁻³⁰ or apixaban (four studies)³¹⁻³⁴ with enoxaparin in total hip

replacement (eight studies)^{20 22-24 27 29 30 33} or total knee replacement (eight studies).^{19 21 25 26 28 31 32 34} Of these, 36 149 patients were randomised to dosages of the new anticoagulant (n=19 481) or control treatment (n=16 668) required for inclusion in the meta-analysis and therefore comprised the intention to treat population. Most of the studies (n=11) used the European enoxaparin regimen as comparator.^{19 20 22-25 27 29 30 32 33} Three of the eight publications of rivaroxaban trials did not include the specific method of sequence generation,^{27 29 30} and this information was obtained from the sponsor after request. Fifteen of the 16 studies were double blind clinical trials,^{19-26 28-34} scoring 5 points (maximum score) on the Jadad scale, and were judged to be at low risk of bias (adequate sequence generation or allocation concealment, double blinding, and clear reporting of loss to follow-up). The remaining (dose finding) study with rivaroxaban scored 3 (because it was an open label study).²⁷ In all cases adjudication of events was blinded.

Patients' characteristics were homogeneous across the trials, with age ranging between 61 and 68 years, a predominance of women, and body weight between 75 and 84 kg (table 2↓).

Rates of symptomatic venous thromboembolism in the enoxaparin control group were low and similar across studies. Therefore data on symptomatic venous thromboembolism were considered suitable for meta-analysis. However, major bleeding rates reported in the four pivotal RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes) studies with rivaroxaban²³⁻²⁶ were 7-8 times lower than those in the enoxaparin groups of the remaining studies, which was attributed to the exclusion of most wound bleedings from the definition of major bleeding, as previously reported.⁸⁻¹⁰ This issue prevented the pooling of data on major bleeding reported in the publications of the RECORD studies. However, the major bleeding rates in the RECORD studies without excluding major wound bleedings were reported in an FDA review,³⁸ and were similar to the major bleeding rates of the remaining studies. Finally, we used the major bleeding data of RECORD studies from the FDA in the main analysis and major bleeding data from the publications as an additional sensitivity analysis.

Primary efficacy outcome

Rivaroxaban was associated with a significant reduction in risk of symptomatic venous thromboembolism compared with enoxaparin (relative risk 0.48, 95% confidence interval 0.31 to 0.75; P=0.001) (fig 2↓). Compared with enoxaparin, neither dabigatran (0.71, 0.23 to 2.12; P=0.54) nor apixaban (0.82, 0.41 to 1.64; P=0.57) reduced the risk of symptomatic venous thromboembolism (fig 2).

No evidence of statistical heterogeneity for symptomatic venous thromboembolism was found among studies comparing rivaroxaban or apixaban with enoxaparin. However, there was evidence of statistical heterogeneity for symptomatic venous thromboembolism among the dabigatran trials (P=0.01; I²=73%) (fig 2). The source of heterogeneity could not be identified after investigating dabigatran daily dose, enoxaparin regimen, type of surgery, adjudicating committee, or the presence of an outlier study. The effect on symptomatic venous thromboembolism compared with enoxaparin was similar with dabigatran doses of 220 mg (0.70, 0.18 to 2.76; P=0.61) and 150 mg (0.86, 0.31 to 2.35; P=0.63).

After including symptomatic venous thromboembolism events that occurred during follow-up, the results were similar than those of the main analysis (not including post-treatment events):

rivaroxaban (0.53, 0.37 to 0.77; P=0.0008), dabigatran (0.90, 0.45 to 1.80; P=0.76), and apixaban (0.69, 0.30 to 1.57; P=0.37) compared with enoxaparin.

the use of the fixed effects model led to closer confidence intervals than those obtained using random effects, suggesting a lower risk of symptomatic venous thromboembolism with rivaroxaban than with dabigatran (0.53, 0.29 to 0.99) or apixaban (0.51, 0.27 to 0.96).

Publication bias

The visual inspection of funnel plots showed no evidence of publication bias (see supplementary figure A11).

Role of funding

All studies were sponsored by pharmaceutical companies. The sponsor was responsible for the collection and statistical analysis of the data. In all cases the sponsor was involved in the design and oversight of the study with or without the collaboration of a scientific committee, and at least one of the authors of the publications were employees of the sponsor.

Discussion

Rivaroxaban seems more effective than enoxaparin in preventing symptomatic venous thromboembolism but at the cost of an increase in clinically relevant bleeds. These results were consistent across different studies, without evidence of heterogeneity.

Dabigatran seems at least as effective as enoxaparin in the risk of symptomatic venous thromboembolism, but the results are noticeable by heterogeneity and wide confidence intervals. Surrogate venographic data on major and total venous thromboembolism indicates that the high dose (220 mg) is consistently non-inferior to enoxaparin. The low dabigatran dose (150 mg) may provide an alternative in patients with anticipated increased exposure to dabigatran,³⁹ such as those aged more than 75 years and those with moderate renal impairment.⁵ In our meta-analysis, the risk of clinically relevant bleeding was not significantly different between dabigatran and enoxaparin. The upper limit of the 95% confidence interval, however, indicates that a relative risk of clinically relevant bleeding with dabigatran versus enoxaparin by 35% cannot be excluded.

Apixaban was associated with a lower rate of clinically relevant bleeding than enoxaparin, mainly in knee pivotal studies, but associated with an increase in cases of pulmonary embolism, also in knee pivotal studies. Symptomatic pulmonary embolism occurs earlier in knee replacement surgery than in hip replacement surgery,^{40 41} which might theoretically result in an increase in risk of early pulmonary embolism if the first dose of the anticoagulant is delayed. Whether the benefit in bleeding and the numerical increase in pulmonary embolism in knee studies are a chance finding or due to the delay of the first apixaban dose about 18 hours after surgery (mean in pivotal trials) deserves further scrutiny. Doctors may consider the potential benefits of earlier anticoagulation for venous thromboembolism prophylaxis as well as the risks of post-surgical bleeding in deciding on when to administer within the approved time window (12 to 24 hours after surgery for apixaban).⁷

Sensitivity analyses

Sensitivity analyses were consistent with those of the main analysis for the direct comparisons between the new anticoagulants and enoxaparin on symptomatic venous thromboembolism, clinically relevant bleeding, and the net clinical endpoint, regardless of the assumption of the statistical model and study quality, phase, or duration (see supplementary tables A1-3). Acceptance of the definition for major bleeding as reported in the publications (accepting the exclusion of major wound bleedings in the RECORD studies), had a significant impact on the apparent efficacy and safety of rivaroxaban, as it would have been declared superior to enoxaparin in the net clinical endpoint (0.68, 0.50 to 0.91; $P=0.01$) (table A4 of the supplementary appendix). In sensitivity analyses of indirect comparisons (tables A5 to A7 of the supplementary appendix),

Our meta-analysis also shows that the definition of major bleeding may have a significant impact on the apparent safety of the anticoagulants and that even difficult to perceive changes in the definitions may lead to different conclusions in the benefit-risk balance.

Strengths of the review

Our study represents the most comprehensive meta-analysis of new oral anticoagulants carried out in total hip or knee replacement surgery up to date. It is based on data from more than 30 000 patients enrolled in 16 randomised clinical trials, 15 of them using a double blind design and all including an independent and blinded assessment of outcomes. The studies were published between 2005 and 2011 and evidence of publication bias was lacking. Sensitivity analyses suggest that the results are robust. It is unlikely that a clinical trial comparing two new oral anticoagulants in total hip or knee replacement surgery would be carried out in the near future. Therefore our results provide a useful estimate of expected relative differences on clinically relevant events between rivaroxaban, dabigatran, and apixaban in total hip or knee replacement surgery.

Limitations of the review

Our systematic review has limitations. The main efficacy outcome in our study (symptomatic venous thromboembolism) was a secondary outcome in all studies. Therefore the results on symptomatic venous thromboembolism are exploratory. Nevertheless, all events were adjudicated blindly and independently, which adds robustness to the results obtained. However, symptomatic venous thromboembolism events are more representative of what would be expected in standard clinical practice than are venographic (mainly asymptomatic) events.⁸ Direct comparisons between rivaroxaban or apixaban versus enoxaparin for major or total venous thromboembolism are based on studies in which venograms were adjudicated by the same committee (Gothenburg committee in the rivaroxaban studies and Hamilton committee in the apixaban studies), whereas two committees (Gothenburg and Holland) were used in the dabigatran studies. Given the double blind adjudication, it can be reasonably expected that the calculated relative risk of direct comparisons would have provided an unbiased estimate. However, we decided not to report indirect comparisons on major and total venous thromboembolism because the differences in venographic assessment reported between different adjudicating committees⁴²⁻⁴⁵ was considered a factor that might bias the indirect comparison.⁴⁶

At the time of translating the results from these clinical trials into practice, some considerations are necessary. In absolute terms it is expected that patients in standard clinical practice would have a higher risk for symptomatic venous thromboembolism and bleeding than those included in clinical

trials, because of the exclusion criteria applied in clinical trials (that is, severe renal or hepatic insufficiency, chronic use of vitamin K antagonists, concomitant treatment with non-steroidal anti-inflammatory drugs of long half life, strong CYP3A4 inhibitors, history of bleeding, and so on), as well as by other differences in personal characteristics.⁴⁷⁻⁴⁸ It is worth mentioning that the risk of bleeding increases with age and in other special situations to a greater extent than does the risk of symptomatic venous thromboembolism.⁴⁸ Therefore one of the main uncertainties about the use of the new anticoagulants is related to their real bleeding risk in standard clinical practice,⁴⁹⁻⁵¹ which emphasises the need for appropriate use according to product labelling to minimise such risk.⁵⁻⁷

Conclusions

Our meta-analysis indicates that a higher efficacy of the new type of anticoagulants was generally associated with a higher bleeding tendency, but the anticoagulants did not differ significantly for efficacy and safety.

Contributors: AG-O, AIT-F, EV-C, and MLS-G conceived and designed the study. AG-O and AIT-F collected the data. AG-O carried out the statistical analysis and drafted the manuscript. EV-C supervised the study. All authors analysed and interpreted the data and critically revised the manuscript for important intellectual content. The contents of this study are solely the responsibility of the authors and do not necessarily represent the official view of their institutions or any other party. AG-O and EV-C are the guarantors.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Data sharing: No additional data available.

- Cohen AT, Agnelli G, Anderson FA, Arcelus JI, Bergqvist D, Brecht JG, et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. *Thromb Haemost* 2007;98:756-64.
- Mackman N. Triggers, targets and treatments for thrombosis. *Nature* 2008;451:914-8.
- Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, et al. Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines (8th ed). *Chest* 2008;133(6 suppl):S381-453.
- White RH, Zhou H, Romano PS. Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. *Thromb Haemost* 2003;90:446-55.
- European Medicines Agency. Pradaxa®—summary of product characteristics. 2011. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000829/WC500041059.pdf.
- European Medicines Agency. Xarelto®—summary of product characteristics. 2011. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000944/WC500057108.pdf.
- European Medicines Agency. Eliquis®—summary of product characteristics. 2011. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002148/WC500107728.pdf.
- Gómez-Outes A, Lecumberri R, Pozo C, Rocha E. New anticoagulants: focus on venous thromboembolism. *Curr Vasc Pharmacol* 2009;7:309-29.
- Gómez-Outes A, Suárez-Gea ML, Blázquez-Pérez A, Pozo-Hernández C, Vargas-Castrillón E. Rivaroxaban versus enoxaparin after total knee arthroplasty. *Lancet* 2009;374:682.
- Dahl OE, Quinlan DJ, Bergqvist D, Eikelboom JW. A critical appraisal of bleeding events reported in venous thromboembolism prevention trials of patients undergoing hip and knee arthroplasty. *J Thromb Haemost* 2010;8:1966-75.
- Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1-12.
- Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700.
- Cochran WG. The combination of estimates from different experiments. *Biometrics* 1954;10:101-29.
- Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clin Trials* 1986;7:177-88.

- 16 Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959;22:719-48.
- 17 The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan) [Computer program]. Version 5.1; Copenhagen, 2011.
- 18 Wells GA, Sultan SA, Chen L, Khan M, Coyle D. Indirect treatment comparison [computer program]. Version 1.0. Canadian Agency for Drugs and Technologies in Health; Ottawa, 2009.
- 19 Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, et al. 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.
- 20 Eriksson BI, Dahl OE, Rosencher N, Kurth AA, van Dijk CN, Frostick SP, et al. 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.
- 21 The RE-MOBILIZE Writing Committee. Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. *J Arthroplasty* 2009;24:1-9.
- 22 Eriksson BI, Dahl OE, Huo MH, Kurth AA, Hantel S, Hermansson K, et al. Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II). A randomised, double-blind, non-inferiority trial. *Thromb Haemost* 2011;105:721-9.
- 23 Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. *N Engl J Med* 2008;358:2765-75.
- 24 Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet* 2008;372:31-9.
- 25 Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. *N Engl J Med* 2008;358:2776-86.
- 26 Turpie AG, Lassen MR, Davidson BL, Bauer KA, Gent M, Kwong LM, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. *Lancet* 2009;373:1673-80.
- 27 Eriksson BI, Borris LC, Dahl OE, Haas S, Huisman MV, Kakkar AK, et al. Dose-escalation study of rivaroxaban (BAY 59-7939)—an oral, direct Factor Xa inhibitor—for the prevention of venous thromboembolism in patients undergoing total hip replacement. *Thromb Res* 2007;120:685-93.
- 28 Turpie AG, Fisher WD, Bauer KA, Kwong LM, Irwin MW, Kälebo P, et al. BAY 59-7939: an oral, direct factor Xa inhibitor for the prevention of venous thromboembolism in patients after total knee replacement. A phase II dose-ranging study. *J Thromb Haemost* 2005;3:2479-86.
- 29 Eriksson BI, Borris LC, Dahl OE, Haas S, Huisman MV, Kakkar AK, et al. Oral, direct Factor Xa inhibition with BAY 59-7939 for the prevention of venous thromboembolism after total hip replacement. *J Thromb Haemost* 2006;4:121-8.
- 30 Eriksson BI, Borris LC, Dahl OE, Haas S, Huisman MV, Kakkar AK, et al. A once-daily, oral, direct Factor Xa inhibitor, rivaroxaban (BAY 59-7939), for thromboprophylaxis after total hip replacement. *Circulation* 2006;114:2374-81.
- 31 Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. *N Engl J Med* 2009;361:594-604.
- 32 Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P, et al. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. *Lancet* 2010;375:807-15.
- 33 Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, Ramirez LM, et al. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *N Engl J Med* 2010;363:2487-98.
- 34 Lassen MR, Davidson BL, Gallus A, Pineo G, Ansell J, Deitchman D. The efficacy and safety of apixaban, an oral, direct factor Xa inhibitor, as thromboprophylaxis in patients following total knee replacement. *J Thromb Haemost* 2007;5:2368-75.
- 35 Eriksson BI, Dahl OE, Ahnfelt L, Kälebo P, Stangier J, Nehmiz G, et al. Dose escalating safety study of a new oral direct thrombin inhibitor, dabigatran etexilate, in patients undergoing total hip replacement: BISTRO I. *J Thromb Haemost* 2004;2:1573-80.
- 36 Eriksson BI, Dahl OE, Büller HR, Hettiarachchi R, Rosencher N, Bravo ML, et al. A new oral direct thrombin inhibitor, dabigatran etexilate, compared with enoxaparin for prevention of thromboembolic events following total hip or knee replacement: the BISTRO II randomized trial. *J Thromb Haemost* 2005;3:103-11.
- 37 Fuji T, Fujita S, Ujihira, Sato R. Dabigatran etexilate prevents venous thromboembolism after total knee arthroplasty in Japanese patients with a safety profile comparable to placebo. *J Arthroplasty* 2010;25:1267-74.
- 38 FDA Cardiovascular & Renal Drugs Advisory Committee. Meeting ID: 2009-4418. www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/cardiovascularandrenaldrugsadvisorycommittee/ucm181524.pdf.
- 39 Dahl OE, Kurth AA, Rosencher N, Noack H, Clemens A, Eriksson BI. Thromboprophylaxis with dabigatran etexilate in patients over seventy-five years of age with moderate renal impairment undergoing or knee replacement. *Int Orthop* 2012;36:741-8.
- 40 Kearon C. Natural history of venous thromboembolism. *Circulation* 2003;107(23 suppl 1):I22-30.
- 41 Björnarå BT, Gudmundsen TE, Dahl OE. Frequency and timing of clinical venous thromboembolism after major joint surgery. *J Bone Joint Surg Br* 2006;88:386-91.
- 42 Trkulja V, Kolundzic R. Rivaroxaban vs dabigatran for thromboprophylaxis after joint-replacement surgery: exploratory indirect comparison based on meta-analysis of pivotal clinical trials. *Croat Med J* 2010;51:113-23.
- 43 Loke YK, Kwok CS. Dabigatran and rivaroxaban for prevention of venous thromboembolism—systematic review and adjusted indirect comparison. *J Clin Pharm Ther* 2011;36:111-24.
- 44 Maratea D, Fadda V, Trippoli S, Messori A. Prevention of venous thromboembolism after major orthopedic surgery: indirect comparison of three new oral anticoagulants. *J Thromb Haemost* 2011;9:1868-70.
- 45 Quinlan DJ, Eikelboom JW, Dahl OE, Eriksson BI, Sidhu PS, Hirsh J. Association between asymptomatic deep vein thrombosis detected by venography and symptomatic venous thromboembolism in patients undergoing elective hip or knee surgery. *J Thromb Haemost* 2007;5:1438-43.
- 46 Glennly AM, Altman DG, Song F, Sakaravitch C, Deeks JJ, D'Amico R, et al. Indirect comparisons of competing interventions. *Health Technol Assess* 2005;9:1-134.
- 47 Waddell J, Johnson K, Hein W, Raabe J, FitzGerald G, Turibio F. Orthopaedic practice in total hip arthroplasty and total knee arthroplasty: results from the Global Orthopaedic Registry (GLORY). *Am J Orthop (Belle Mead NJ)* 2010;39(9 suppl):5-13.
- 48 Deitelzweig SB, Lin J, Lin G. Preventing venous thromboembolism following orthopedic surgery in the United States: impact of special populations on clinical outcomes. *Clin Appl Thromb Hemost* 2011;17:640-50.
- 49 Jensen CD, Steval A, Partington PF, Reed MR, Muller SD. Return to theatre following total hip and knee replacement, before and after the introduction of rivaroxaban: a retrospective cohort study. *J Bone Joint Surg Br* 2011;93:91-5.
- 50 Legrand M, Mateo J, Aribaud A, Ginisty S, Eftekhari P, Huy PT, et al. The use of dabigatran in elderly patients. *Arch Intern Med* 2011;171:1285-6.
- 51 European Medicines Agency updates on safety of Pradaxa (EMA/CHMP/903767/2011). Press release, 18 Nov 2011. www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/11/WC500117818.pdf.

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Tables

Table 1 | Characteristics of included randomised controlled trials and study treatments

Drug, trial	No in sample	Type of surgery	Trial phase	Dose, treatment duration (timing of first dose in relation to surgery)		Design of randomised controlled trial; adjudicating committee	Jadad score	Day of venography	Follow-up (days)
				Experimental drug	Control drug				
Dabigatran:									
RE-MODEL ¹⁹	2101	Total knee replacement	III	Dabigatran 220 mg or 150 mg once daily, 6-10 days (1-4 hours)	Enoxaparin 40 mg once daily, 6-10 days (about 12 hours*)	Double blind; Gothenburg	5	6-10	90
RE-NOVATE ²⁰	3493	Total hip replacement	III	Dabigatran 220 mg or 150 mg once daily, 28-35 days (1-4 hours)	Enoxaparin 40 mg once daily, 28-35 days (about 12 hours*)	Multicentre, double blind; Holland	5	33	94
RE-MOBILIZE ²¹	2615	Total knee replacement	III	Dabigatran 220 mg or 150 mg once daily, 12-15 days (8-12 hours)	Enoxaparin 30 mg twice daily, 12-15 days (12-24 hours)	Double blind; Gothenburg	5	14	90
RE-NOVATE II ²²	2055	Total hip replacement	III	Dabigatran 220 mg once daily, 28-35 days (1-4 hours)	Enoxaparin 40 mg once daily, 28-35 days (about 12 hours*)	Double blind; Holland	5	32	90
Rivaroxaban:									
RECORD1 ²³	4541	Total hip replacement	III	Rivaroxaban 10 mg once daily, 35d (6 hours)	Enoxaparin 40 mg once daily, 35 days (about 12 hours*)	Double blind; Gothenburg	5	36	66-71
RECORD2 ²⁴	2509	Total hip replacement	III	Rivaroxaban 10 mg once daily, 31-39 days (6 hours)	Enoxaparin 40 mg once daily, 14 days (about 12 hours*)+placebo 30 days	Double blind; Gothenburg	5	32-40	62-75
RECORD3 ²⁵	2531	Total knee replacement	III	Rivaroxaban 10 mg once daily, 10-14 days (6 hours)	Enoxaparin 40 mg once daily, 10-14 days (about 12 hours*)	Double blind; Gothenburg	5	11-15	41-50
RECORD4 ²⁶	3148	Total knee replacement	III	Rivaroxaban 10 mg once daily, 10-14 days (6 hours)	Enoxaparin 30 mg twice daily, 10-14 days (12-24 hours)	Double blind; Gothenburg	5	11-15	40-49
PROOF OF CONCEPT ²⁷	641	Total hip replacement	Ila	Rivaroxaban 2.5, 5, 10, 20, or 30 mg twice daily, rivaroxaban 30 mg once daily, 5-9 days (6-8 hours)†	Enoxaparin 40 mg once daily, 5-9 days (about 12 hours*)	Open label; Gothenburg	3	5-9	38-68
ODIXA KNEE ²⁸	621	Total knee replacement	Iib	Rivaroxaban 2.5, 5, 10, 20, or 30 mg twice daily, 5-9 days (6-8 hours)†	Enoxaparin 30 mg twice daily, 5-9 days (12-24 hours)	Double blind; Gothenburg	5	5-9	37-67
ODIXA HIP (twice daily) ²⁹	722	Total hip replacement	Iib	Rivaroxaban 2.5, 5, 10, 20, or 30 mg twice daily, 5-9 days (6-8 hours)†	Enoxaparin 40 mg once daily, 5-9 days (about 12 hours*)	Double blind; Gothenburg	5	5-9	38-68
ODIXA HIP (once daily) ³⁰	873	Total hip replacement	Iib	Rivaroxaban 10, 20, or 30 mg once daily, 5-9 days (6-8 hours)†	Enoxaparin 40 mg once daily, 5-9 days (about 12 hours*)	Double blind; Gothenburg	5	6-10	35-69
Apixaban:									
ADVANCE-1 ³¹	3195	Total knee replacement	III	Apixaban 2.5 mg twice daily, 10-14 days (12-24 hours)	Enoxaparin 30 mg twice daily, 12 days (12-24 hours)	Double blind; Hamilton	5	10-14	70-84
ADVANCE-2 ³²	3057	Total knee replacement	III	Apixaban 2.5 mg twice daily, 10-14 days (12-24 hours)	Enoxaparin 40 mg once daily, 10-14 day (about 12 hours*)	Double blind; Hamilton	5	10-14	70-84
ADVANCE-3 ³³	5407	Total hip replacement	III	Apixaban 2.5 mg twice daily, 35 days (12-24 hours)	Enoxaparin 40 mg once daily, 35 days (about 12 hours*)	Double blind; Hamilton	5	32-38	90-100

Table 1 (continued)

Drug, trial	No in sample	Type of surgery	Trial phase	Dose, treatment duration (timing of first dose in relation to surgery)		Design of randomised controlled trial; adjudicating committee	Jadad score	Day of venography	Follow-up (days)
				Experimental drug	Control drug				
APROPOS ³⁴	1238	Total knee replacement	2b	Apixaban 5, 10, or 20 mg once daily, 2.5, 5, or 10 mg twice daily, 10-14 days (12-24 hours)‡	Enoxaparin 30 mg twice daily, 10-14 days (about 12 hours*) or warfarin (international normalised ratio 1.8-3.0§)	Double blind; Hamilton	5	10-14	42

*Administered preoperatively; other first doses were administered postoperatively.

†Only data pertaining to 10 mg total daily dose (5 mg twice daily or 10 mg once daily) were included in the meta-analysis.

‡Only data pertaining to 5 mg total daily dose (2.5 mg twice daily or 5 mg once daily) were included in the meta-analysis.

§Only data pertaining to 40 mg once daily dose control group were included in the meta-analysis.

Table 2 | Characteristics of patients, surgery, and concomitant treatments*

Drug, trial	Participants mean age (years), % women, mean weight (kg)	History of venous thromboembolism (%)	Use of neuraxial anaesthesia (%)	Surgery duration (minutes)	Use of elastic compression stockings	Use of intermittent pneumatic compression	Use of acetylsalicylic acid/NSAID
Dabigatran:							
RE-MODEL ¹⁹	68, 69, 82	NA	78	90	Allowed	Prohibited	Allowed: acetylsalicylic acid <160 mg and NSAID of no long half life
RE-NOVATE ²⁰	64, 56, 78	3	76	87	Allowed	Prohibited	Allowed: acetylsalicylic acid <160 mg and NSAID of no long half life
RE-MOBILIZE ²¹	66, 58, 88	NA	48	90	Allowed	Prohibited	Allowed: acetylsalicylic acid <160 mg and NSAID if half life <17 hours
RE-NOVATE II ²²	62, 50, 80	2	77	79	NA	Prohibited	NA
Rivaroxaban:							
RECORD1 ²³	63, 56, 78	2	70	91	NA	Prohibited	Allowed
RECORD2 ²⁴	62, 53, 75	1	71	93	NA	Prohibited	Allowed
RECORD3 ²⁵	68, 67, 81	4	79	97	NA	Prohibited	Allowed
RECORD4 ²⁶	65, 64, 84	2	81	100	NA	Prohibited	Allowed
PROOF OF CONCEPT ²⁷	64, 54, 79	NA	73	NA	Allowed	Prohibited	Allowed if half life <17 hours
ODIXA KNEE ²⁸	66, 55, 89	NA	53	91	Allowed	Prohibited	Allowed if half life <17 hours
ODIXA HIP (twice daily) ²⁹	65, 59, 77	NA	70	82	Allowed	Prohibited	Allowed if half life <17 hours
ODIXA HIP (once daily) ³⁰	66, 64, 75	NA	62	84	NA	Prohibited	Allowed if half life <17 hours
Apixaban:							
ADVANCE-1 ³¹	66, 62, 87	4	87	95	NA	NA	Allowed if half life <17 hours
ADVANCE-2 ³²	67, 74, 78	2	84	95	NA	NA	Allowed if half life <17 hours
ADVANCE-3 ³³	61, 55, 80	2	68	90	NA	NA	Allowed if half life <17 hours
APROPOS ³⁴	67, 52, 83	NA	54	78	NA	NA	NA

NSAID=non-steroidal anti-inflammatory drug; NA=not available.

Table 3| Symptomatic venous thromboembolism, clinically relevant bleeding, and net clinical endpoint by type of surgery

Variables	No of events/No in group		Relative risk (95%CI)	Weight (%)	P value*
	New anticoagulant	Enoxaparin			
Symptomatic venous thromboembolism					
Dabigatran:					
Hip ^{20 22}	23/3367	10/2181	0.78 (0.05 to 12.35)	42.5	0.83
Knee ^{19 21}	25/3141	19/1575	0.56 (0.16 to 1.98)	57.5	
Rivaroxaban:					
Hip ^{23 24 27 29 30}	11/3888	27/3990	0.52 (0.18 to 1.45)	35.6	0.93
Knee ^{25 26 28}	21/2940	44/2946	0.49 (0.29 to 0.83)	64.4	
Apixaban:					
Hip ³³	4/2708	10/2699	0.40 (0.13 to 1.27)	23	0.14
Knee ^{31 32 34}	28/3437	23/3277	1.08 (0.56 to 2.06)	77	
Clinically relevant bleeding					
Dabigatran:					
Hip ^{20 22}	178/3367	87/2181	1.22 (0.95 to 1.58)	51.8	0.36
Knee ^{19 21}	162/3141	79/1575	1.01 (0.74 to 1.39)	48.2	
Rivaroxaban:					
Hip ^{23 24 27 29 30}	186/3888	152/3990	1.25 (0.90 to 1.75)	59.6	0.90
Knee ^{25 26 28}	123/2940	96/2946	1.29 (0.99 to 1.67)	40.4	
Apixaban:					
Hip ³³	131/2708	138/2699	0.95 (0.75 to 1.19)	52.2	0.09
Knee ^{31 32 34}	103/3437	143/3277	0.71 (0.55 to 0.91)	47.8	
Net clinical endpoint					
Dabigatran:					
Hip ^{20 22}	81/3367	38/2181	1.26 (0.80 to 1.98)	49.3	0.06
Knee ^{19 21}	58/3141	41/1575	0.71 (0.48 to 1.05)	50.7	
Rivaroxaban:					
Hip ^{23 24 27 29 30}	86/3888	94/3990	0.92 (0.60 to 1.41)	53.2	0.76
Knee ^{25 26 28}	71/2940	84/2946	0.85 (0.60 to 1.19)	46.8	
Apixaban:					
Hip ³³	29/2708	29/2699	1.00 (0.60 to 1.66)	32.8	0.70
Knee ^{31 32 34}	58/3437	62/3277	0.88 (0.62 to 1.26)	67.2	

*Random effects model, subgroup differences.

Table 4| Indirect comparisons between rivaroxaban, dabigatran, and apixaban*

Outcomes	Relative risk (95% CI)		
	Rivaroxaban v dabigatran	Rivaroxaban v apixaban	Apixaban v dabigatran
Symptomatic venous thromboembolism	0.68 (0.21 to 2.23)	0.59 (0.26 to 1.33)	1.16 (0.31 to 4.28)
Clinically relevant bleeding	1.12 (0.87 to 1.44)	1.52 (1.19 to 1.95)	0.73 (0.57 to 0.94)
Major bleeding	1.37 (0.79 to 2.39)	1.59 (0.84 to 3.02)	0.86 (0.41 to 1.83)
Net clinical endpoint	0.95 (0.61 to 1.48)	0.96 (0.66 to 1.40)	0.99 (0.61 to 1.61)

*Random effects model, events while receiving treatment.

Table 5| Direct and indirect comparisons: absolute difference in events per 1000 patients treated*

Comparison	Risk difference (95% CI)			
	Symptomatic venous thromboembolism	Clinically relevant bleeding	Major bleeding	Net clinical endpoint
Direct comparisons:				
Rivaroxaban v enoxaparin	-5 (-9 to -1)	9 (2 to 17)	4 (-0.4 to 8)	-3 (-9 to 3)
Dabigatran v enoxaparin	-2 (-9 to 5)	5 (-4 to 13)	-1 (-6 to 5)	-1 (-9 to 7)
Apixaban v enoxaparin	-1 (-4 to 2)	-8 (-15 to -1)	-1 (-7 to 5)	-1 (-6 to 3)
Indirect comparisons:				
Rivaroxaban v dabigatran	-3 (-11 to 4)	5 (-7 to 16)	4 (-2 to 11)	-2 (-12 to 9)
Rivaroxaban v apixaban	-4 (-9 to 1)	18 (7 to 28)	5 (-2 to 12)	-2 (-9 to 6)
Apixaban v dabigatran	1 (-7 to 8)	-13 (-24 to -2)	0 (-8 to 7)	0 (-9 to 9)

*Random effects model, events while receiving treatment.

Figures

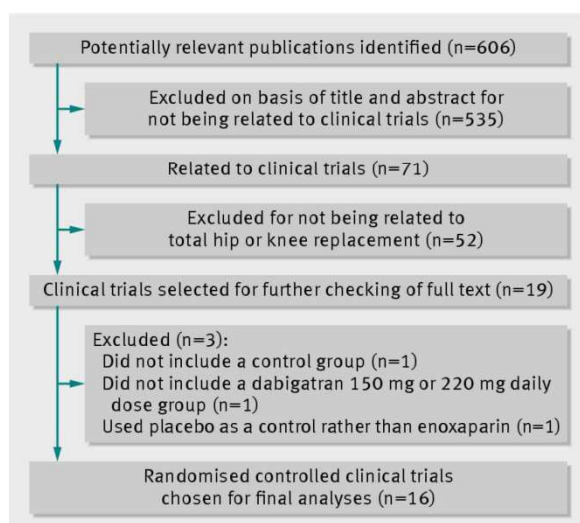


Fig 1 Study identification, selection, and exclusions

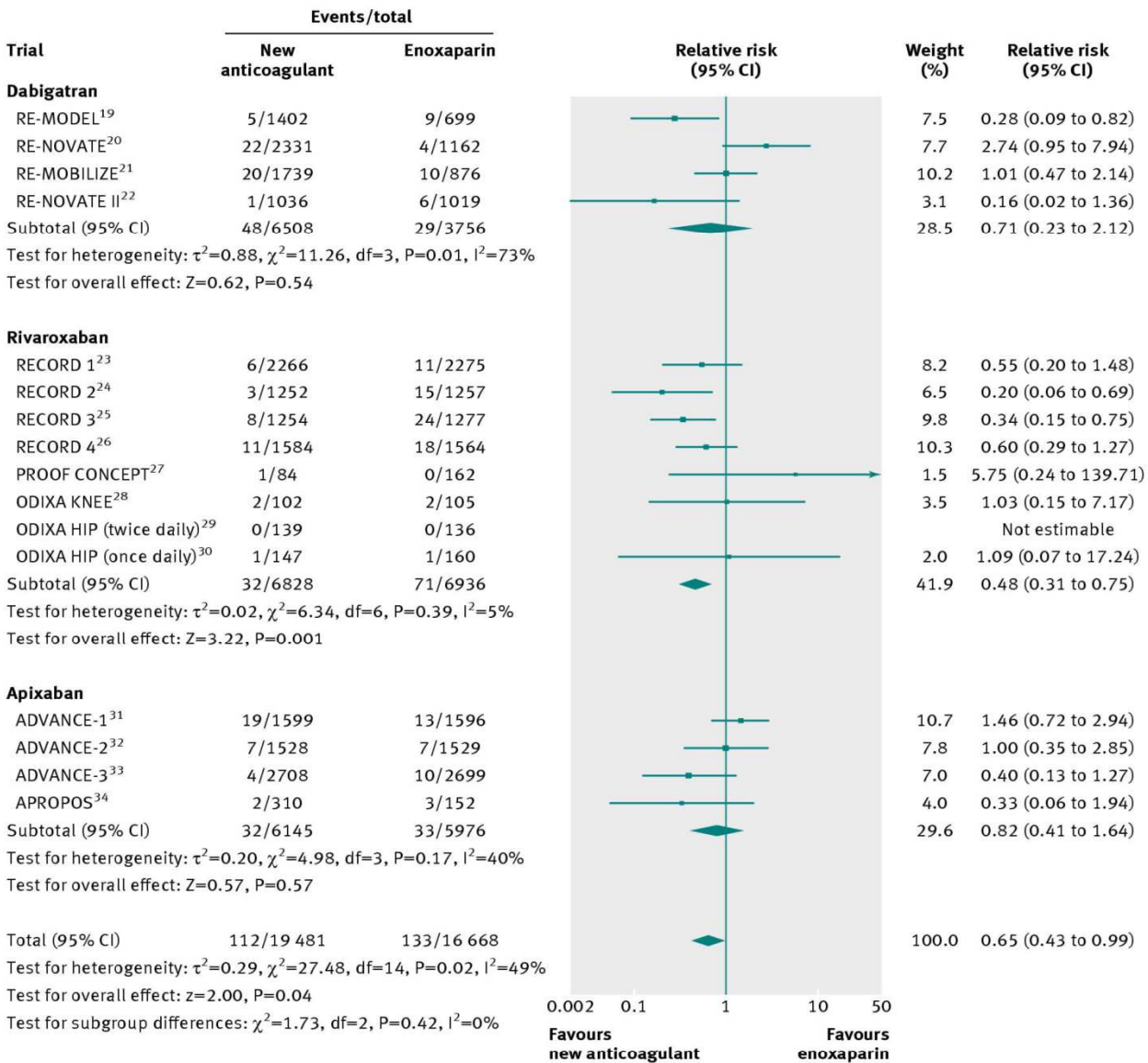


Fig 2 Symptomatic venous thromboembolism

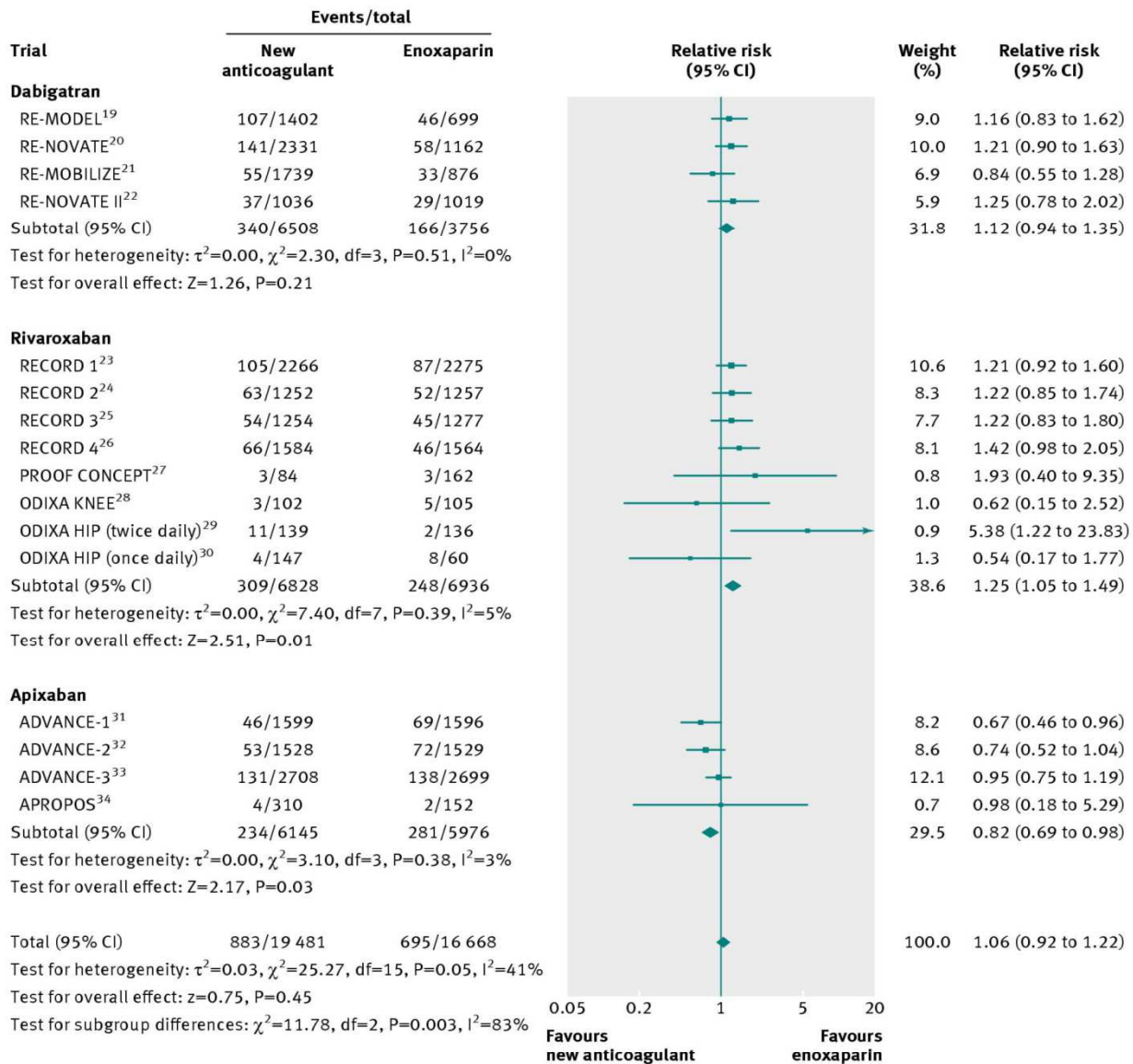


Fig 3 Clinically relevant bleeding

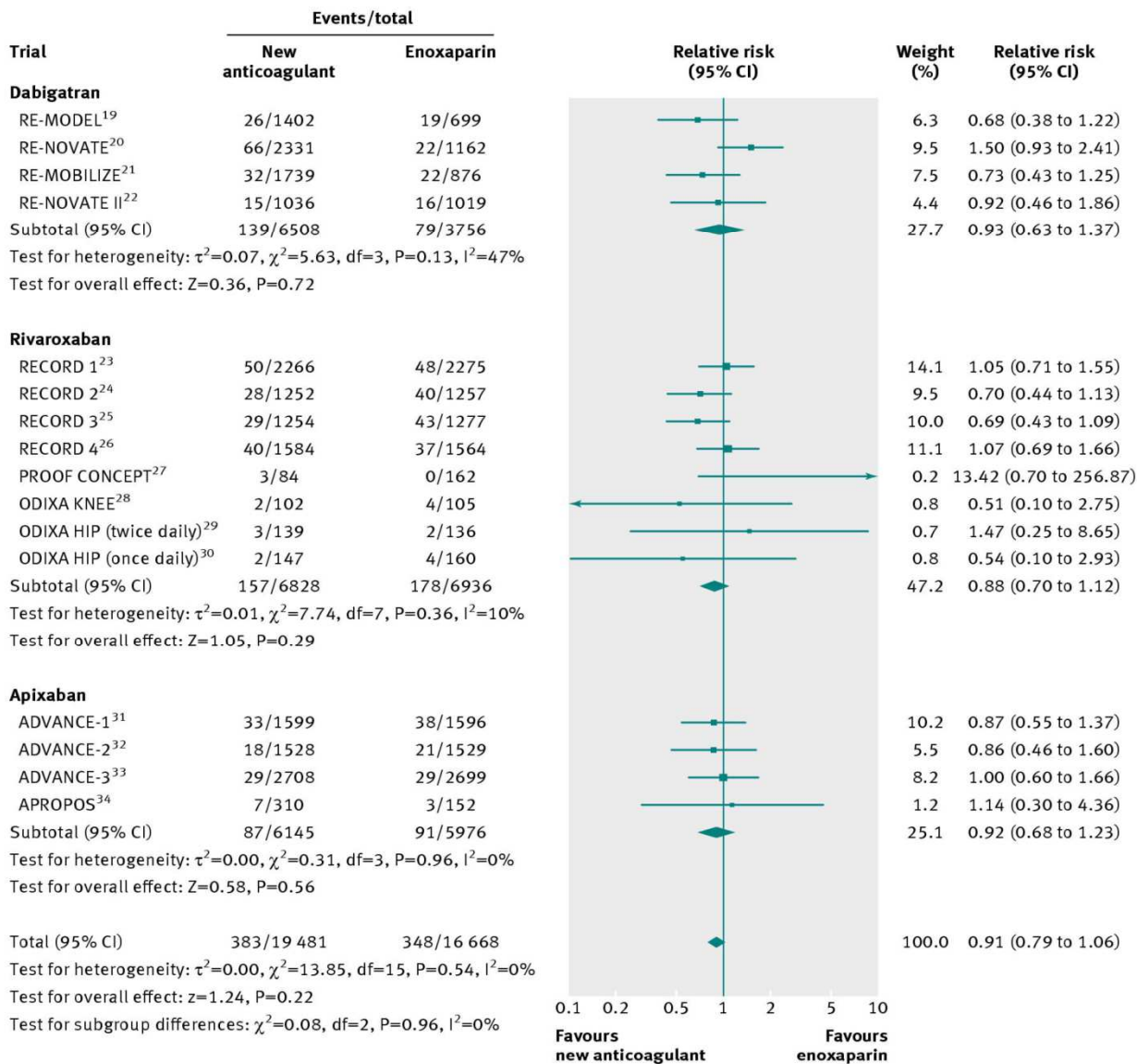


Fig 4 Net clinical endpoint