This is the peer reviewed author accepted manuscript (post print) version of a published work that appeared in final form in:

Huxley, Nicola, Sidhu, Verinder, Kelly, Thu-Lan, Pratt, Nicole L, Graves, Stephen E, Buchbinder, Rachelle, Adie, Sam, Cashman, Kara, Ackerman, Ilana, de Steiger, Richard, Lorimer, Michelle, Naylor, Justine M, Harris, Ian A, Harris, Anthony 2024 'Cost-effectiveness of enoxaparin versus aspirin in the prevention of venous thromboembolism after total hip or knee arthroplasty: an analysis from the CRISTAL cluster-randomized trial', Bone and Joint Journal, vol. 106-B, no. 6, pp. 589-595

This un-copyedited output may not exactly replicate the final published authoritative version for which the publisher owns copyright. It is not the copy of record. This output may be used for non-commercial purposes.

The final definitive published version (version of record) is available at:
https://doi.org/10.1302/0301-620X.106B6.BJJ-2023-0783.R2

Persistent link to the UniSA Research Outputs Repository:
https://researchoutputs.unisa.edu.au/11541.2/40398

General Rights

Copyright and moral rights for the publications made accessible in the UniSA Research Outputs Repository are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the persistent link identifying the publication in the UniSA Research Outputs Repository

If you believe that this document breaches copyright, please contact us and provide details. We will remove access to the work immediately and investigate your claim.

TITLE PAGE

Title: Cost effectiveness of enoxaparin versus aspirin in the prevention of venous thromboembolism after total hip or knee arthroplasty: an analysis from the CRISTAL, cluster randomised trial

Word Count: 3949 words (including abstract and references)

Research Group Authorship: CRISTAL Economic Analysis Study Group

Full list of authors, contributions and affiliations:

1. Nicola Huxley, PhD (Data Curation, Formal analysis, Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review and editing)
    i. Centre for Health Economics, Monash Business School, Monash University, Melbourne, Victoria, Australia
2. Verinder S. Sidhu, MS (Conceptualization, Investigation, Methodology, Project Administration, Writing – original draft, Writing – review and editing)
    i. School of Clinical Medicine, South Western Sydney Clinical School, Faculty of Medicine and Health, UNSW Sydney, Sydney, New South Wales, Australia
    ii. Whitlam Orthopaedic Research Centre, Ingham Institute for Applied Medical Research
3. Thu-Lan Kelly, PhD (Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review and editing)

i. Clinical and Health Sciences, Quality Use of Medicines Pharmacy Research Centre, University of South Australia, Adelaide, South Australia, Australia

4. Nicole Pratt, PhD (Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review and editing)
    i. Clinical and Health Sciences, Quality Use of Medicines Pharmacy Research Centre, University of South Australia, Adelaide, South Australia, Australia
5. Stephen E. Graves, DPhil (Conceptualization, Investigation, Methodology, Project administration, Writing – review and editing)
    i. Australian Orthopaedic Association National Joint Replacement Registry, Adelaide, South Australia, Australia
6. Rachelle Buchbinder, PhD (Conceptualization, Investigation, Methodology, Project administration, Writing – review and editing)
    i. School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia
7. Sam Adie, PhD (Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – review and editing)
    i. School of Clinical Medicine, UNSW Medicine & Health, St George & Sutherland Clinical Campuses, Faculty of Medicine and Health, UNSW Sydney, New South Wales, Australia
8. Kara Cashman, GradDip (Data curation, Formal analysis, Project administration, Writing – original draft, Writing – review and editing)
    i. South Australian Health and Medical Research Institute, Adelaide, South Australia, Australia

9. Ilana N. Ackerman, PhD (Conceptualization, Investigation, Project administration, Writing – review and editing)
    i. School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia
10. Richard de Steiger, PhD (Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review and editing)
    i. Department of Surgery, Epworth Healthcare, University of Melbourne, Melbourne, Victoria, Australia
11. Michelle Lorimer, BSc(Hons) (Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Writing – review and editing)
    i. South Australian Health and Medical Research Institute, Adelaide, South Australia, Australia
12. Justine Maree Naylor, PhD (Conceptualization, Investigation, Methodology, Project administration, Writing – review and editing)
    i. School of Clinical Medicine, South Western Sydney Clinical School, Faculty of Medicine and Health, UNSW Sydney, Sydney, New South Wales, Australia
    ii. Whitlam Orthopaedic Research Centre, Ingham Institute for Applied Medical Research
13. Ian A. Harris, PhD (Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review and editing)
    i. School of Clinical Medicine, South Western Sydney Clinical School, Faculty of Medicine and Health, UNSW Sydney, Sydney, New South Wales, Australia

ii. Whitlam Orthopaedic Research Centre, Ingham Institute for Applied Medical Research

iii. Institute of Musculoskeletal Health, School of Public Health, The University of Sydney, Sydney, New South Wales, Australia

14. Anthony Harris, MSc (Conceptualization, Formal analysis, Methodology, Project administration, Supervision, Writing – original draft, Writing – review and editing)

i. Centre for Health Economics, Monash Business School, Monash University, Melbourne, Victoria, Australia

Corresponding Author:

Dr Verinder Sidhu (corresponding author)

Address: Ingham Institute, 1 Campbell Street, Liverpool, New South Wales, Australia, 2170

Email: verinder.s.sidhu@gmail.com

Phone: +61 422 167 435

ABSTRACT

Background

The aim of this study was to evaluate the health care costs and benefits of enoxaparin compared to aspirin in the prevention of symptomatic venous thromboembolism (VTE) after total hip arthroplasty (THA) or total knee arthroplasty (TKA) using data from the CRISTAL trial**.**

Methods

This trial-based economic analysis reports value for money as incremental cost per quality-adjusted life-year (QALY) gained in 2022 Australian dollars, compared to a single threshold value of $70,000 per QALY. Event costs were estimated based on occurrence of VTEs and bleeds, and published guidelines for treatment. Unit costs were taken from Australian sources. QALYs were estimated using CRISTAL 6-month follow-up data. Sensitivity analyses are presented around the cost of VTE treatment and extending the analysis to 2 years with 5% discounting of costs and benefits.

Results

The CRISTAL trial found that enoxaparin was more effective than aspirin in preventing symptomatic VTE within 90 days of THA or TKA (risk difference 1.97% (95%CI 0.54%, 3.41%, p=0.007)). The additional cost after a THA or TKA was $83 (95%CI $68, $97) for enoxaparin; and enoxaparin resulted in an additional 0.002 (95%CI -0.002, 0.005) QALYs. Incremental cost per QALY gained was $50,567 (95%CI $15,513, dominated) for enoxaparin. We can be

60% confident that the incremental cost per QALY does not exceed the willingness-to-pay threshold of $70,000. Increasing the cost of VTE treatment and extension of costs and consequences to 2 years suggested greater confidence that enoxaparin is value for money (70% and 63% confidence respectively).

Conclusion

This analysis provides strong evidence that enoxaparin thromboprophylaxis following THA or TKA reduced VTEs, but weak evidence of net economic benefits over aspirin. If the value of avoiding VTEs is high, and there is a strong likelihood of VTE-related health impairments, we can be more confident that enoxaparin is cost-effective compared to aspirin.

Trial Registration: ACTRN12618001879257

INTRODUCTION

The use of aspirin for symptomatic venous thromboembolism (VTE) prophylaxis after primary total hip arthroplasty (THA) or total knee arthroplasty (TKA) has increased in over the past decade.[1] While aspirin is cheaper and easier to administer, there is limited evidence that aspirin alone is effective.[1,2] The CRISTAL cluster-randomized crossover trial found that enoxaparin (a low-molecular weight heparin (LMWH)) was superior to aspirin in preventing symptomatic VTE within 90 days of primary THA or TKA for osteoarthritis.[3,4] However, aspirin is cheaper, and it remains unclear whether enoxaparin represents value for money, given its higher direct cost.

Evidence of the cost-effectiveness of LMWH compared to aspirin is mixed.[5-8] There appears to be uncertainty around the quality of life benefits of LMWH over aspirin.[9] A modelled cost-effectiveness analysis of thromboprophylaxis in THA and TKA in Australia compared LMWH to intermittent pneumatic compression and direct oral anticoagulants (DOACs) excluding aspirin, and found that LMWH was dominated by DOACs, that were less costly and resulted in better patient outcomes as measured by quality adjusted life years (QALYs).[6]

The main aim of this paper is to evaluate the cost-effectiveness of enoxaparin compared to aspirin in the prevention of symptomatic VTE after primary THA or TKA within a 6-month randomized controlled trial (the CRISTAL trial), and ~~if the results are robust, to~~ an extended simulated follow up at 2 years.

METHODS

Analysis

No health economic analysis plan was written prior to the economic evaluation. The study takes a health system perspective in a pre-planned intention to treat analysis of trial data. The CRISTAL cluster randomized trial reported VTEs up to 90 days after hip or knee arthroplasty and quality of life for all patients at baseline and 6 months. Australian hospitals that performed more than 250 THA or TKA procedures per annum were recruited between April 15th 2019 and August 12th, 2019. Thirty-one hospitals were randomized to initially deliver aspirin (15 hospitals) or enoxaparin (16 hospitals) to all hip or knee arthroplasty patients. Once the sample size was met for the first arm, hospitals crossed over to the alternate treatment arm. Patient enrolment commenced on April 20th 2019 and ceased on December 18th 2020. Patients were excluded from receiving either study drug if on long-term anticoagulation preoperatively (a DOAC, warfarin or dual antiplatelet therapy) or if they had a medical contraindication to either drug. The trial was approved by all relevant ethics committees prior to commencing. It was funded by a four-year Medical Research Futures Fund grant (Australian Government). The funder had no role in the trial design, statistical analyses or interpretation of results. The prespecified population in the economic analysis[3] was primary THA or TKA for osteoarthritis[4,10] whose VTE status was reported (93.8% enoxaparin, 95.4% aspirin).

Clinical outcomes of interest included any symptomatic VTE or bleeding complications within 90 days of surgery. Data for these outcomes were patient-reported and collected online and were verified by contacting the patient's treating clinician.

Cost effectiveness was calculated as: (i) the incremental cost per VTE avoided compared to a threshold social willingness-to-pay for a VTE, (ii) the incremental cost per quality adjusted life year (QALY)~~;~~ at 6 months post-surgery compared to a threshold cost per QALY. For ease of analysis and interpretation these two measures were compared to a threshold willingness-to-pay through incremental net money value of benefits (INMB), calculated by subtracting the incremental cost from the incremental QALYs (or VTEs) valued at the social willingness-to-pay for a QALY (or a VTE). No discounting was applied to costs or benefits as they were assumed to accrue within 12 months. The INMB was calculated across a range of willingness-to-pay values with an initial assumed threshold maximum social willingness-to-pay for a QALY of $70,000 ($US 47,000) based on the likelihood of previous public reimbursements of medical technologies and surveys.[11,12] An equivalent willingness-to-pay per VTE avoided was estimated, based on previously published estimates relating VTE avoided to QALY gain.[6] The resulting threshold was $3,850 per VTE avoided.

The robustness of the conclusions was explored through several sensitivity analyses ~~to~~: (i) variation in the cost of VTE treatment; (ii) inclusion of costs and benefits of potential sequelae after 6 months, and (iii) alternative specifications of the statistical model, including cluster-level summary measures of costs and outcomes adjusted for the incomplete crossover, and alternative statistical models estimated to test for the effect of skewness on cost estimates. These sensitivity analyses are detailed in Appendices 3 and 4.

Cost Data

Costs are presented as 2022 Australian dollars. Costs were calculated for each patient based on individual clinical events collected as part of the trial report and include only health care costs.

The total cost for each patient was calculated as the sum of the cost of individual component events over 3 months. A summary of the cost inputs is presented in Table 1. All costs are from the health system perspective and do not include societal costs such as time off work. Unit costs were taken from Australian sources (Pharmaceutical Benefits Scheme, PBS; Medicare Benefits Schedule, MBS; Australian Refined Diagnosis Related Groups, AR-DRG), and where necessary inflated to 2022 prices. Individual time on treatment was not available and therefore average time on treatment was based on number of intended doses minus the average missed doses. Enoxaparin was assumed to require a one-off administration cost and that further doses would be self-administered by the patient or their family members.

The cost of a VTE event was calculated as the cost for a course of treatment with a DOAC (weighted price of apixaban or rivaroxaban), with time on VTE treatment based on the American Society of Hematology 2020 guidelines for management of VTE.[13] Factors that affected time on DOACs were based on the joint replaced and patients' prior VTE experience,[13] with courses of treatment assumed to last up to a maximum of a year for this analysis. Hospitalisation after VTE was not recorded and therefore the base case assumed no hospitalisation as a consequence of VTE, as per the ASH guidelines.[13]

The event cost of treatment for bleeding complications resulting in readmission was based on AR-DRG weights applied to the cost of hospital services.[14] For patients with a bleeding

complication that did not require readmission, the price was based on a GP attendance and a specialist visit.

Quality of Life

Health related quality of life during the trial ~~were~~ was estimated using a multi-attribute utility instrument (EQ-5D-5L),[15] with scores reported at baseline and at 6-month follow up in CRISTAL and converted to utilities using Australian valuations.[16] QALYs of patients in each arm during the trial period (6 months) were calculated as the area under the curve between baseline and 6-month utilities for each of the imputed datasets.

Missing data

Where >10% data was missing, baseline data were imputed using the mean imputation method for all patients and follow-up data multiply imputed separately for each arm, creating 5 datasets by chained equations using predictive mean matching with three nearest neighbours by treatment arm.

Statistical Analysis

Incremental costs and VTE incidence were estimated linear regressions of outcome on VTE prevention therapy and order of therapy in the hospital, with hospital clustering on the standard errors to allow for intragroup correlation. Incremental QALYs were estimated from linear regressions of VTE prevention therapy and order of therapy in the hospital controlling for EQ-5D-5L utility at baseline. Results from the five multiple imputed datasets were combined using Rubin's rules.[17] Formulae for the regression models for costs, VTE incidence and QALYS and sensitivity analyses are presented in Appendices 2-4.

Cost Effectiveness Analysis

We report 95% confidence intervals and *p*-values for between group differences in costs, VTEs and QALYs, and plot cost-effectiveness acceptability curves (CEACs) as one minus the one sided *p*-values at which the program would have positive INMB over a range willingness-to-pay thresholds.[18] Willingness-to-pay thresholds were varied from $0 to $20,000 for incremental cost per VTE avoided and $0 to $100,000 for incremental cost per QALY. The CEAC can be interpreted as the degree of confidence that the data supports the cost effectiveness of enoxaparin.[18-21] INMBs and CEACs were calculated using existing Stata programs.[22] All analyses were performed using StataMP version 17 (StataCorp LLC) and R (R Foundation for Statistical Computing Platform) version 4.1.3.

RESULTS

The CRISTAL trial included 9,203 patients who were randomized to commence enoxaparin or aspirin after undergoing primary THA or TKA and who reported VTE status. Patient characteristics at baseline were similar across the enoxaparin and aspirin groups (Appendix 1) and no further adjustments were made, in line with the comparative effectiveness publication.[3] Follow-up data was missing for VTE location (1 patient), prior VTE status in pulmonary embolism patients, PE, (5 patients), bleeding event or type (25 patients), utility at baseline (448 patients), and utility at 6-month follow up (1,096). However, utility reporting at 6 months was similar across groups (88.0% in the enoxaparin arm, 88.2% in the aspirin arm), suggesting treatment allocation was unlikely to be the cause of missing data. Utilities were multiply imputed as previously described, matched on utility at baseline, sex, age, surgery location (hip or knee) and whether a VTE occurred during trial. Results using the imputed data are presented here.

Incremental results are presented in Table 3. Enoxaparin resulted in an increase of $93 (95%CI $88, $97) in VTE prevention costs compared to aspirin and a saving in VTE treatment of -$4 (95%CI -$7, -$1). Enoxaparin was also associated with a statistically insignificant reduction in treatment costs of bleeding complications compared to aspirin (-$6, 95%CI -$19, $8). This was largely driven by lower rates of re-admission for patients on enoxaparin who developed a bleed (27% vs 41% in the aspirin arm). Patients admitted to hospital following a bleed had a much higher estimated cost of treatment ($10,504) compared with those who were not admitted ($85), but as bleeds were only present in a small number of patients (0.3% of the aspirin arm and 0.4% of the enoxaparin arm), the cost

savings were very small. The total additional cost in the enoxaparin arm was $83 (95%CI $68, $97) compared to aspirin.

Incremental VTEs were -0.016 for enoxaparin versus aspirin (95%CI -0.026, -0.005) and incremental QALYs gained for enoxaparin were estimated to be 0.002 (95%CI -0.002, 0.005). Incremental cost per VTE avoided was $5,319 (95%CI $3,008 $15,931) and incremental cost per QALY gained was $50,567 (95%CI $15,513, dominated: more costly and less effective).

Figure 1 presents the CEACs for enoxaparin. There is 85% confidence that the incremental cost per VTE avoided does not exceed the ~~At the~~$3,850 willingness-to-pay threshold. With increasing ~~a~~ willingness-to-pay to avoid a VTE, enoxaparin becomes more cost effective. There is 95% confidence that the incremental cost per VTE avoided does not exceed a willingness-to-pay of $12,027 for enoxaparin compared to aspirin.

In terms of quality of life, enoxaparin has a 60% probability ~~at a~~ of not exceeding the willingness-to-pay threshold of $70,000 per QALY gained, compared to aspirin, but there is no willingness-to-pay threshold that offers 95% confidence.

Sensitivity Analyses

Full results of the sensitivity analyses are presented in Appendices 3 and 4. Including potential sequalae at 2 years suggests greater confidence that the incremental cost per QALY of enoxaparin does not exceed the $70,000 threshold (63% in Figure A3.3, Appendix 3).

If PE patients all accrued a cost of hospital stay then, we can be 70% confident that the incremental cost per QALY of enoxaparin does not exceed the $70,000 threshold (Figure

A3.2.b, Appendix 3), or 61% confident that the incremental cost per QALY of enoxaparin does not exceed the willingness-to-pay $3,850 per VTE avoided (Figure A3.2.a, Appendix 3) at 6 months.

Estimating cost per VTE avoided based on cluster summary level analysis rather than patient level analysis produced similar CEACs for enoxaparin (see Appendix 4).

DISCUSSION

While the CRISTAL trial found that enoxaparin was superior to aspirin in preventing symptomatic VTE within 90 days of primary total hip or knee arthroplasty, the cost offsets associated with the reduction in VTE treatment did not outweigh the higher cost of enoxaparin even when potential sequelae within 2 years were included. The majority of VTE events in the CRISTAL trial (70%) were the less costly below-knee DVTs,[3] which might account for the low health care cost savings.

An advantage of this study is that the costs and outcomes are directly informed by patient data within a randomized trial, rather than the approach taken in most of the literature of estimating a modelled cohort from published averages of comparative costs and outcomes from potentially heterogenous populations. However, data limitations did require assumptions to be made with regards cost and QALY estimates. In particular, CRISTAL enrolment was stopped early due to superior effectiveness of enoxaparin over aspirin at the 21-month interim analysis; while the trial was still powered to detect differences in VTE, it was never powered to make statistically valid inferences about differences in EQ-5D scores, costs or net benefits that may have resulted from a reduction in DVTs. Further, the extension to 2 years may also not capture all the costs and consequences of the potential sequalae with long term effects.

Total costs (both within trial and extended to 2 years) were lower than reported in the other recent published cost-effectiveness analyses, likely due to fewer DVTs, PEs and bleeds within 90 days and a shorter time horizon than previously published models.[5-8] Compared to a recent Australian analysis [6] the CRISTAL study also had fewer patients with prior VTEs and a lower rate of THA versus TKA which might result in fewer complications following surgery.

There were also differences in the acquisition cost of enoxaparin and aspirin across the studies, likely due to differences in country and year. As such, the results should be applied to other settings with some caution.

The CRISTAL data showed similar 6-month utility improvement to UK National Health Service (NHS) reported estimates[23] with an increase pre-surgery and 6 months post-surgery of 0.436 vs 0.445 for THA and 0.315 vs 0.311 TKA for NHS and CRISTAL respectively. Further, the results of this study are similar to Smith et al,[5] where enoxaparin was associated with a 0.001 QALY gain versus aspirin in TKA patients over a similar time period in a US setting. This suggests there is broader generalisability of our results to other settings. It is possible that gains in quality of life from avoided VTEs have been underestimated in the CRISTAL trial ~~if~~ to the extent that VTE and their effects on quality of life occurred in the first two months after surgery and patients recovered before their first follow-up. This will have biased the results against enoxaparin and in favour of aspirin. There was considerable variation in the incremental QALY gain at 2 years between patients in the CRISTAL trial reflected in the wide confidence intervals but this is consistent with a wide variation in quality of life between patients in long-term studies of LMWH versus aspirin.[7,8] Subgroups at higher risk of VTE, for example patients with a history of VTE[3], may benefit more from enoxaparin, a potential scenario not captured in this analysis. Further, as the trial only considered monotherapy, the cost-effectiveness analysis could not explore the utility gains of patients receiving combination therapies.

Given the imprecision in estimating QALY gain, the cost per VTE avoided is a potential proxy measure of value for money.[9] The attractiveness of enoxaparin thromboprophylaxis then depends on the value placed on VTE avoided and number of patients hospitalized with a

VTE. At higher monetary values of VTE avoided there is reasonable confidence that the incremental cost per VTE avoided for enoxaparin will not exceed the threshold, while at lower values (willingness-to-pay < $3,000 per VTE avoided), and low rates of hospitalization, aspirin appears more attractive. Other modelled thromboprophylaxis cost effectiveness studies in the literature assume that all cases of VTE are hospitalized[5,7,8,24] but our base case adheres to ASH guidelines,[13] which do not recommend hospitalization. If all patients with PE were hospitalized,[7] there is more confidence that the incremental cost per VTE (and per QALY) for enoxaparin versus ~~over~~ aspirin does not exceed chosen willingness-to-pay thresholds.

CONCLUSIONS

This analysis is the first trial-based economic comparison of enoxaparin and aspirin for thromboprophylaxis following arthroplasty and provides strong evidence that enoxaparin thromboprophylaxis following THA or TKA reduced VTEs, but weak evidence of economic benefits over aspirin. The cost savings from reduced VTE did not outweigh the additional direct cost of enoxaparin, but if the value of avoiding VTEs is high, and if there is a strong likelihood of recurrent VTEs, PTS or CTEPH we can be more confident that enoxaparin is cost-effective compared to aspirin.

REFERENCES

1. Abdel MP, Meneghini RM, Berry DJ. Current Practice Trends in Primary Hip and Knee Arthroplasties Among Members of the American Association of Hip and Knee Surgeons: An Update During the COVID-19 Pandemic. *J Arthroplasty*. Jul 2021;36(7S):S40-S44 e3. doi:10.1016/j.arth.2021.01.080
2. Matharu GS, Kunutsor SK, Judge A, Blom AW, Whitehouse MR. Clinical Effectiveness and Safety of Aspirin for Venous Thromboembolism Prophylaxis After Total Hip and Knee Replacement: A Systematic Review and Meta-analysis of Randomized Clinical Trials. *JAMA Intern Med*. Mar 1 2020;180(3):376-384. doi:10.1001/jamainternmed.2019.6108
3. CRISTAL Study Group. Effect of Aspirin vs Enoxaparin on Symptomatic Venous Thromboembolism in Patients Undergoing Hip or Knee Arthroplasty: The CRISTAL Randomized Trial. *JAMA*. 2022;328(8):719-727. doi:10.1001/jama.2022.13416
4. Sidhu VS, Kelly TL, Pratt N, et al. CRISTAL (a cluster-randomised, crossover, non-inferiority trial of aspirin compared to low molecular weight heparin for venous thromboembolism prophylaxis in hip or knee arthroplasty, a registry nested study): statistical analysis plan. *Trials*. Aug 24 2021;22(1):564. doi:10.1186/s13063-021-05486-0
5. Smith SR, Katz JN, Losina E. Cost-Effectiveness of Alternative Anticoagulation Strategies for Postoperative Management of Total Knee Arthroplasty Patients. *Arthritis Care Res (Hoboken)*. Dec 2019;71(12):1621-1629. doi:10.1002/acr.23803
6. Torrejon Torres R, Saunders R, Ho KM. A comparative cost-effectiveness analysis of mechanical and pharmacological VTE prophylaxis after lower limb arthroplasty in Australia. *J Orthop Surg Res*. 2019;14(1):93-93. doi:10.1186/s13018-019-1124-y
7. Dawoud DM, Wonderling D, Glen J, et al. Cost-Utility Analysis of Venous Thromboembolism Prophylaxis Strategies for People Undergoing Elective Total Hip and Total Knee Replacement Surgeries in the English National Health Service. *Front Pharmacol*. 2018;9:1370-1370. doi:10.3389/fphar.2018.01370
8. Schousboe JT, Brown GA. Cost-effectiveness of low-molecular-weight heparin compared with aspirin for prophylaxis against venous thromboembolism after total joint arthroplasty. *J Bone Joint Surg Am*. Jul 17 2013;95(14):1256-64. doi:10.2106/JBJS.L.00400
9. Yates AJ, Jr. Prophylaxis against venous thromboembolism after arthroplasty: establishing value requires more than one perspective. Commentary on an article by John T. Schousboe, MD, PhD, and Gregory A. Brown, MD, PhD: "Cost-effectiveness of low-molecular-weight heparin compared with aspirin for prophylaxis against venous thromboembolism after total joint arthroplasty". *J Bone Joint Surg Am*. Jul 17 2013;95(14):e102 1-2. doi:10.2106/jbjs.M.00430
10. Sidhu VS, Graves SE, Buchbinder R, et al. CRISTAL: protocol for a cluster randomised, crossover, non-inferiority trial of aspirin compared to low molecular weight heparin for venous thromboembolism prophylaxis in hip or knee arthroplasty, a registry nested study. *BMJ Open*. Nov 6 2019;9(11):e031657. doi:10.1136/bmjopen-2019-031657
11. Harris AH, Hill SR, Chin G, Li JJ, Walkom E. The role of value for money in public insurance coverage decisions for drugs in Australia: a retrospective analysis 1994-2004. *Med Decis Making*. Sep-Oct 2008;28(5):713-22. doi:10.1177/0272989X08315247
12. Shiroiwa T, Sung YK, Fukuda T, Lang HC, Bae SC, Tsutani K. International survey on willingness-to-pay (WTP) for one additional QALY gained: what is the threshold of cost effectiveness? *Health Econ*. Apr 2010;19(4):422-37. doi:10.1002/hec.1481
13. Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv*. Oct 13 2020;4(19):4693-4738. doi:10.1182/bloodadvances.2020001830
14. The Independent Hospital Pricing Authority. National Efficient Price Determination 2021–22. Accessed 13 February, 2022. https://www.ihacpa.gov.au/resources/national-efficient-price-determination-2021-22

15. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of Life Research*. 2011/12/01 2011;20(10):1727-1736. doi:10.1007/s11136-011-9903-x
16. Norman R, Cronin P, Viney R. A pilot discrete choice experiment to explore preferences for EQ-5D-5L health states. *Appl Health Econ Health Policy*. Jun 2013;11(3):287-98. doi:10.1007/s40258-013-0035-z
17. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. John Wiley & Sons, Inc.; 1987.
18. Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves--facts, fallacies and frequently asked questions. *Health Econ*. May 2004;13(5):405-15. doi:10.1002/hec.903
19. Briggs A. *Handling Uncertainty in Economic Evaluation and Presenting the Results*. Economic Evaluation in Health Care: Merging Theory with Practice. Oxford University Press; 2001.
20. Glick DHA, Doshi DJA, Sonnad DSS, Polsky DD. 140Comparing cost and effect: point estimates for cost-effectiveness ratios and net monetary benefit. In: Glick HA, Doshi JA, Sonnad SS, Polsky D, eds. *Economic Evaluation in Clinical Trials*. Oxford University Press; 2014. Accessed 2/13/2023. https://doi.org/10.1093/med/9780199685028.003.0007
21. Nixon RM, Wonderling D, Grieve RD. Non-parametric methods for cost-effectiveness analysis: the central limit theorem and the bootstrap compared. *Health Econ*. Mar 2010;19(3):316-33. doi:10.1002/hec.1477
22. Glick DHA. Programs for Estimating Sampling Uncertainty for Cost-Effectiveness Analysis. Accessed 9th February, 2023. https://drhenryglick.com/sampling-uncertainty-for-cost-effectiveness-analysis/
23. NHS Digital. *Finalised Patient Reported Outcome Measures (PROMs) in England - April 2014 to March 2015*. 2016. Accessed 18th April 2023. https://digital.nhs.uk/data-and-information/publications/statistical/patient-reported-outcome-measures-proms/finalised-patient-reported-outcome-measures-proms-in-england-april-2014-to-march-2015
24. Saunders R, Comerota AJ, Ozols A, Torrejon Torres R, Ho KM. Intermittent pneumatic compression is a cost-effective method of orthopedic postsurgical venous thromboembolism prophylaxis. *Clinicoecon Outcomes Res*. 2018;10:231-241. doi:10.2147/ceor.S157306
25. Morgan A, Joshy G, Schaffer A, et al. Rapid and substantial increases in anticoagulant use and expenditure in Australia following the introduction of new types of oral anticoagulants. *PLoS One*. 2018;13(12):e0208824. doi:10.1371/journal.pone.0208824
26. Kahn SR, Shbaklo H, Lamping DL, et al. Determinants of health-related quality of life during the 2 years following deep vein thrombosis. *J Thromb Haemost*. Jul 2008;6(7):1105-12. doi:10.1111/j.1538-7836.2008.03002.x
27. Caprini JA, Botteman MF, Stephens JM, et al. Economic burden of long-term complications of deep vein thrombosis after total hip replacement surgery in the United States. *Value Health*. Jan-Feb 2003;6(1):59-74. doi:10.1046/j.1524-4733.2003.00204.x
28. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health*. Aug 2010;13(5):509-18. doi:10.1111/j.1524-4733.2010.00700.x

TABLES

Table 1. Cost inputs and unit costs

Input parameter	**Enoxaparin arm**	**Aspirin arm**	**Source**
Dose (mg)	40mg daily	100mg daily	CRISTAL protocol [10]
Intended time on treatment (days)			
Hip	35	35	CRISTAL protocol [10]
Knee	14	14	CRISTAL protocol [10]
Average doses missed per patient	3.4	1.9	CRISTAL data
Time on treatment for VTE			
Proximal DVT, PE | no history	4.5 months		American Society of Hematology 2020 guidelines [4]
Proximal DVT, PE | history	12 months		
Below knee DVT	6 weeks		
VTE treatment (%)			
Apixaban	44%		Morgan 2018 (excluding those not listed for this indication) [25]
Rivaroxaban	56%		
VTE treatment schedule			
Apixaban	10mg twice a day for 7 days, then 5mg twice a day for remaining treatment time (proximal VTE, no history 130 days; proximal VTE, history 358 day, below knee DVT 35 days)		Apixaban product information document from Australian Register of Therapeutic Goods
Rivaroxaban	15mg twice daily for 3 weeks, then 20mg once daily for remaining treatment time (proximal VTE, no history 116 days; proximal VTE, history 344 day, below knee DVT 21 days)		Rivaroxaban product information document from Australian Register of Therapeutic Goods
Unit costs			
Enoxaparin ($/dose)	$4.25		DPMQ enoxaparin 8510X, 8639Q $42.50 for 10x40mg syringes

Input parameter	Enoxaparin arm	Aspirin arm	Source
Aspirin ($/dose)		$0.13	DPMQ aspirin 10509J $14.20 for 112x100mg tabs
Enoxaparin administration (one-off)	$17.90		MBS item 3A1
VTE treatment (DOACs)			
Apixaban $/pack	Initiating $50.27 28x5mg Continuing $93.91 60x5mg		DMPQ apixaban 10414D and 2735Y
Rivaroxaban $/pack	Initiating $114.92 42x15mg Continuing $80.55 28x20mg		DMPQs rivaroxaban 2160Q 2268J
Proximal DVT, PE | no history	$452.31		Weighted cost of DOAC treatment for 4.5 months
Proximal DVT, PE | history	$1,134.49		Weighted cost of DOAC treatment for 12 months
Below knee DVT	$168.51		Weighted cost of DOAC treatment for 6 weeks
Event costs			
Bleeding complication, not admitted	$84.50		MBS items 23 (GP attendance) and 105 (specialist subsequent visit)
Bleeding complication, admitted	$10,504.20		NEP 2021-22 prices weighted by 2018-19 AR-DRG codes Major GI bleed (G61A) and Major intracranial injury (B78A)

Table 2. Two year model parameters

Parameter	**Value**	**Source**
Probabilities		
Probability of VTE recurrence| VTE in CRISTAL	8%	Kahn 2008 [26] (31/387 recurrent VTE)
Probability of PTS|DVT in CRISTAL	40%	ASH VTE guidelines (30-50%) and Dawoud 2018 (40%)
Probability of severe PTS|DVT in CRISTAL	9.2%	ASH VTE guidelines (total 5-10%) and Dawoud 2018. (23% of PTs severe)
Probability of PTS|PE	15%	Dawoud 2018
Probability of severe PTS|PE in CRISTAL	3.5%	15% x 23%
Probability of CTEPH| PE in CRISTAL	3.2%	Dawoud 2018
Costs		
Cost of VTE recurrence	$1,134.49	Weighted cost of DOAC treatment for 12 months (based on ASH VTE guidelines to continue treatment indefinitely)
Cost of PTS mild/moderate	Yr 1 $3,733.80 Yr 2: $1,517.55	Caprini 2003 [27] converted with OECD PPP and inflation index to 2022 applied
Cost of PTS severe	Yr 1 $16,986.77 Yr 2: $,1,517.55	Caprini 2003 [27] converted with OECD PPP and inflation index to 2022 applied
Cost of CTEPH (annual)	$12,937.90	Weighted cost of DOAC treatment for 12 months (based on ASH VTE guidelines to continue treatment indefinitely) plus NEP 2021-22 prices weighted by 2018-19 AR-DRG codes Pulmonary embolism major complexity (E61A)
Utility		
Utility from 1 yr	Age based general population utility	Ara and Brazier[28]
PTS mild/moderate disutility	-0.02	Dawoud 2018
PTS severe disutility	-0.07	Dawoud 2018
CTEPH disutility Yr1| PE in CRISTAL	-26%	Dawoud 2018

Table 2. Results of cost and QALY analyses using individual patient data, imputed dataset

	Mean (sd)		Estimated incremental difference [a,b]		
	Enoxaparin	Aspirin	Mean	lower 95%	upper 95%
Costs					
~~VTE prevention~~ Thromboprophylaxis	$96.65 ($43.27)	$2.55 ($1.29)	$92.72	$88.48	$96.95
VTE treatment	$5.05 ($43.53)	$9.78 ($64.94)	-$3.99	-$7.22	-$0.75
Bleed complication[a]	$11.37 ($341.27)	$13.78 ($377.44)	-$5.70	-$19.18	$7.77
Total cost[a]	**$113.07 ($347.49)**	**$26.11 ($383.49)**	**$82.75**	**$68.24**	**$97.26**
Effectiveness					
VTE occurrence	0.018 (0.134)	0.035 (0.183)	-0.016	-0.026	-0.005
QALYs[b]	0.294 (0.118)	0.287 (0.123)	0.002	-0.002	0.005
Incremental cost per VTE avoided			$5,319	$3,008	$15,931
Incremental cost per QALY gained			$50,567	$15,513	Dominated[c]

CI=confidence interval, VTE=venous thromboembolism, QALY=quality adjusted life year, n=9203

a missing event data imputed from average cost for bleed complications by treatment arm

b missing baseline utility data estimated from single imputation by treatment arm, missing 6-month utility data estimated from multiple imputation

c Dominated=enoxaparin was both more costly and less effective

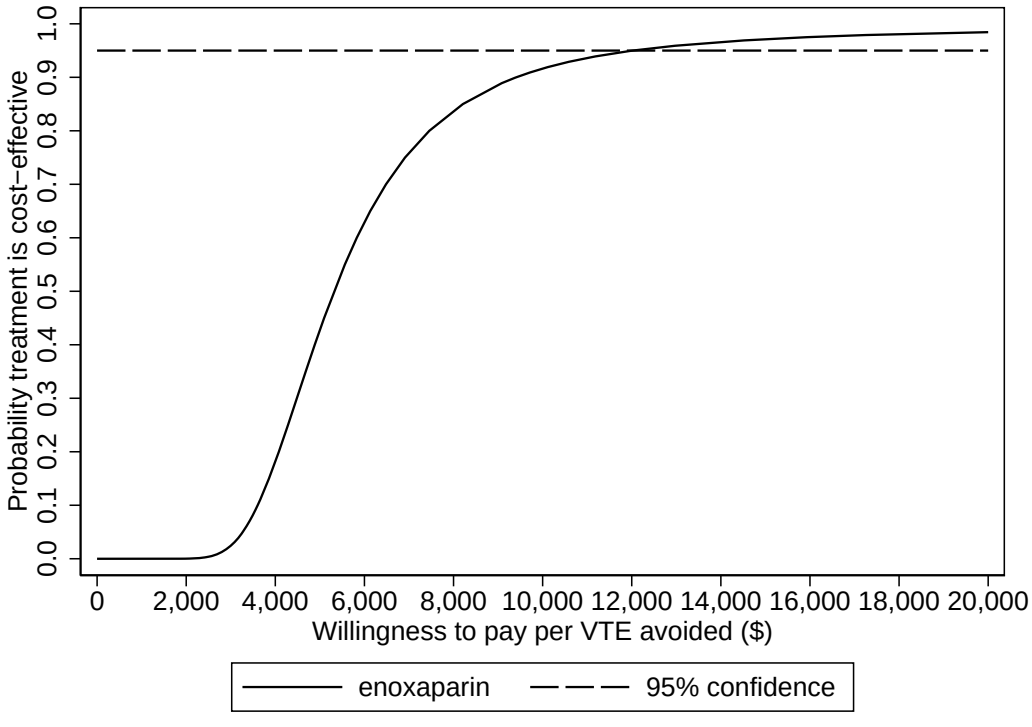
FIGURE LEGENDS

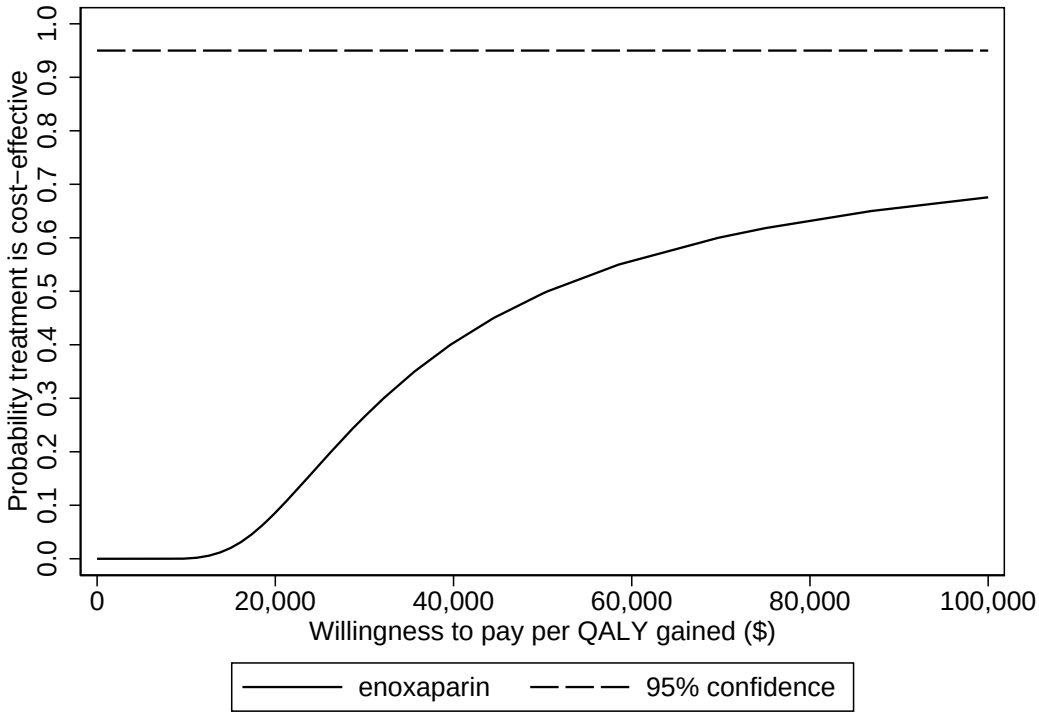
Figure 1. Cost-effectiveness acceptability curves for enoxaparin, main analysis

Incremental cost per VTE avoided	Incremental cost per QALY gained
Base case	
a)	b)

VTE=venous thromboembolism, QALY=quality adjusted life year

Figure 1. Cost-effectiveness acceptability curves for enoxaparin at 2 years


Probability treatment is cost−effective
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
0 2,000 4,000 6,000 8,000 10,000 12,000 14,000 16,000 18,000 20,000
Willingness to pay per VTE avoided ($)
enoxaparin
95% confidence


Probability treatment is cost-effective
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
0
20,000
40,000
60,000
80,000
100,000
Willingness to pay per QALY gained ($)
enoxaparin
95% confidence

SUPPLEMENTARY ANALYSES

Appendix 1

Table A1.1. Baseline characteristics

Patient characteristic	Aspirin	Enoxaparin	p-value	Test
N	5416	3787		
Male, n (%)	2361 (43.6%)	1635 (43.2%)	0.690	Pearson's chi-squared
Age, mean (SD)	67.11 (9.64)	67.57 (9.62)	0.023	Two sample t test
BMI, mean (SD)	31.48 (6.77)	31.55 (7.98)	0.660	Two sample t test
Prior VTE, n (%)	270 (5.0%)	228 (6.0%)	0.043	Pearson's chi-squared
Preoperative utility score, mean (SD)	0.39 (0.34)	0.40 (0.33)	0.200	Two sample t test
Patients receiving THA	2068 (38.2%)	1430 (37.8%)	0.680	Pearson's chi-squared
Treated in crossed over hospital, n (%)	3062 (56.5%)	500 (13.2%)	<0.001	Pearson's chi-squared

N=total number of patients, n=number of patients, SD=standard deviation, BMI=body mass index, VTE=venous thromboembolism, THA=total hip arthroplasty

While age and proportion of patients with prior VTE were statistically different at p=0.05 level, they did not appear to be clinically meaningfully different and the cost effectiveness results were not sensitive to their inclusion. Whether patients attended a hospital before or during the crossover period is controlled for in the base case analysis

Appendix 2

Regression analyses

Costs and VTE incidence were estimated based on a linear regression of each individual patient outcome with an indicator variable for VTE prevention therapy and order of therapy in the hospital, and hospital clustering on the standard errors to allow for intragroup correlation (eqn. 1).

$$y_{kh} = \alpha\beta_0 + \beta_1 \mathrm{A1}_{kh} + \beta_2 \mathrm{A2}_{kh} + \beta_3 \mathrm{E1}_{kh} + \beta_4 \mathrm{E2}_{kh} + \epsilon_{kh} \qquad (1)$$

where y_{kh} = outcome for patient k in hospital h,

with 4 indicator variables representing

treatments $\{\mathrm{A} = \text{aspirin}, \mathrm{E} = \text{enoxparin}\}$ and

whether hospital had yet experienced crossover $\{1 = \text{prior to switching}, 2 = \text{after switching}\}$,

ϵ_{kh} = error for each patient.

Standard errors were clustered over each hospital.

QALYs at 6 months were estimated based on linear regressions on the five multiple imputed datasets combined using Rubin's rules [1] (eqn. 2). The linear regressions modelled each individual patient outcome with an indicator variable for VTE prevention therapy and order of therapy in the hospital, and hospital clustering on the standard errors to allow for intragroup correlation.

$$QALY = \alpha\gamma_0 + \gamma_1 \mathrm{A1}_{kh} + \gamma \mathrm{A2}_{kh} + \gamma_3 \mathrm{E1}_{kh} + \gamma_4 \mathrm{E2}_{kh} + + \gamma_5 U_b + \epsilon_{kh} \qquad (2)$$

where y_{kh} = outcome for patient k in hospital h,

with 4 indicator variables representing

treatments $\{\mathrm{A} = \text{aspirin}, \mathrm{E} = \text{enoxparin}\}$ and

whether hospital had yet experienced crossover $\{1 = \text{prior to switching}, 2 = \text{after switching}\}$,

U_b = utility at baseline, ϵ_{kh} = error for each patient.

Appendix 3

Cost of VTE treatment

To explore the cost of VTE treatment, an additional event cost for hospitalization was applied for all pulmonary embolisms (PEs), based on 2021-22 National Efficiency Price (NEP)[2] weighted by AR-DRG codes E61A and E61B for PE, similar to the approach presented in other models of the cost-effectiveness of VTE prevention post-THA or TKA.[3]

Extension to 2 years

The trial-based analysis was extended to 2 years to simulate the scenario of additional costs and benefits of thromboprophylaxis not captured in the trial. The extension estimated costs and QALYS from potential VTE recurrence, post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH) that may occur as a direct consequence of the initial VTE beyond the 90-day trial follow up to 2 years, based on probabilities reported in published literature. Included parameters are reported in Table 2. Long term events were chosen to align with a recent cost-effectiveness study,3,4 plus with the addition of recurrence of VTE.

The comparison of a 2-year timeframe compared to trial time horizon was done to test if the results of the trial were sensitive to extrapolation of the costs and consequences to a longer time frame and some of the analytical assumptions made in the trial analysis. If the trial results are robust to changes in time frame (and other parameter assumptions) they are not sensitive to the assumptions regarding these long-term costs and consequences.

A decision tree approach for the patient pathway over the two years is described in Figure A3. A decision tree approach was chosen as the least complex structure which retained memory of patient history, and was reasonable over a short time horizon. While up to 50% of people will have longer term complications from VTE,[7] health-related quality of life (HRQoL) tends to improve during follow-up. Most of the improvement occurs in the first 3-6 months after DVT, with scores returning to the population average within 1-2 years.[8] For patients who do not experience PTS or CTEPH, HRQoL the disutility for events from 1 year is assumed to be that of the general population adjusted for age and sex.[9] Disutility for these events was taken from Dawoud et al. 2018.[3]

Costs were calculated per event (further VTE, PTS, CTEPH) based on a maximum of 2 years of management costs. The 2-year costs and QALYs for each patient were estimated from summary average cost and disutility for a patient according to their VTE status at 90 days in CRISTAL with 5% discounting applied to costs and benefits in the second year, in line with Australian guidelines.[10] Parameter inputs are presented in Table A3.

Figure A3.1. Diagram of analysis extended to 2 years

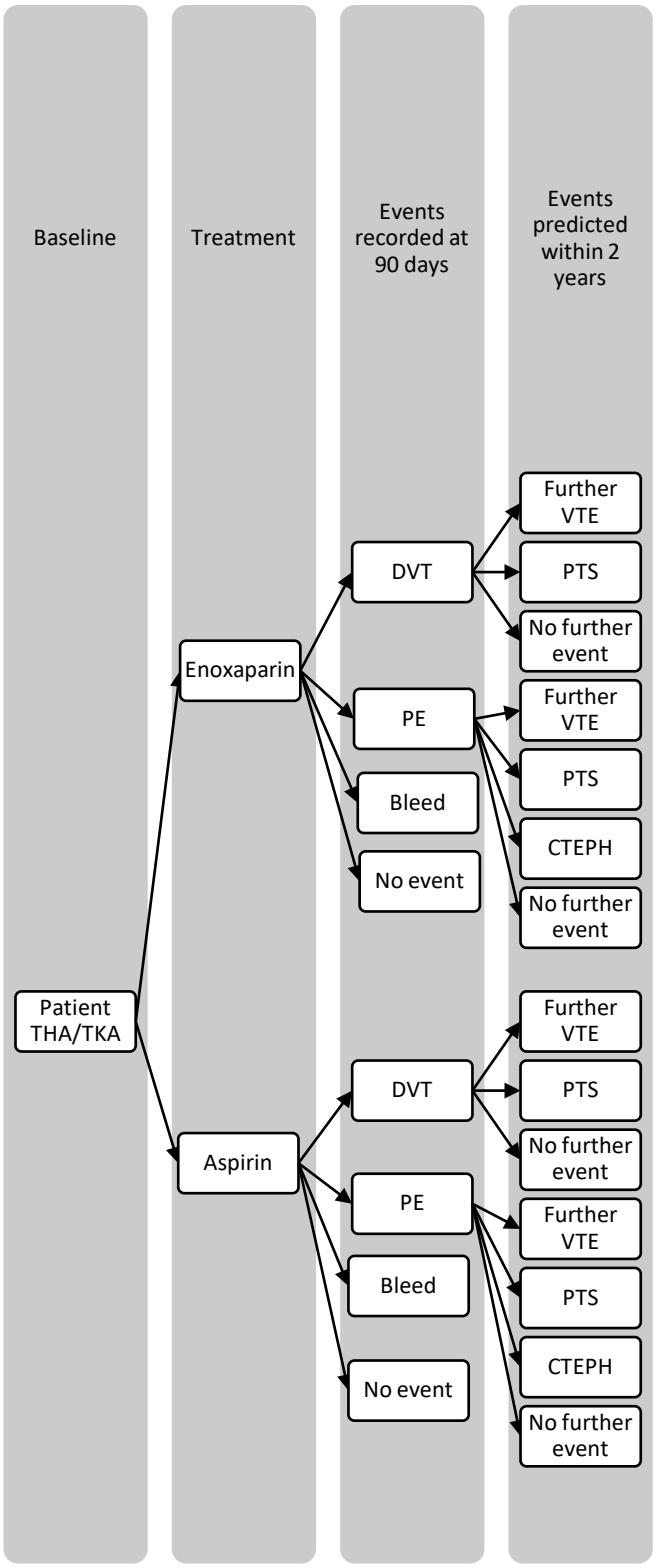


Table A3.1. Two year model parameters

Parameter	Value	Source
Probabilities		
Probability of VTE recurrence| VTE in CRISTAL	8%	Kahn 2008 [8] (31/387 recurrent VTE)
Probability of PTS|DVT in CRISTAL	40%	ASH VTE guidelines (30-50%) and Dawoud 2018 (40%)
Probability of severe PTS|DVT in CRISTAL	9.2%	ASH VTE guidelines (total 5-10%) and Dawoud 2018. (23% of PTS severe)
Probability of PTS|PE	15%	Dawoud 2018
Probability of severe PTS|PE in CRISTAL	3.5%	15% x 23%
Probability of CTEPH| PE in CRISTAL	3.2%	Dawoud 2018
Costs		
Cost of VTE recurrence	$1,134.49	Weighted cost of DOAC treatment for 12 months (based on ASH VTE guidelines to continue treatment indefinitely)
Cost of PTS mild/moderate	Yr 1 $3,733.80 Yr 2: $1,517.55	Caprini 2003 [11] converted with OECD PPP and inflation index to 2022 applied
Cost of PTS severe	Yr 1 $16,986.77 Yr 2: $,1,517.55	Caprini 2003 [11] converted with OECD PPP and inflation index to 2022 applied
Cost of CTEPH (annual)	$12,937.90	Weighted cost of DOAC treatment for 12 months (based on ASH VTE guidelines to continue treatment indefinitely) plus NEP 2021-22 prices weighted by 2018-19 AR-DRG codes Pulmonary embolism major complexity (E61A)
Utility		
Utility from 1 yr	Age based general population utility	Ara and Brazier[9]
PTS mild/moderate disutility	-0.02	Dawoud 2018
PTS severe disutility	-0.07	Dawoud 2018
CTEPH disutility Yr1| PE in CRISTAL	-26%	Dawoud 2018

ASH= American Society of Hematology, CTEPH= Chronic thromboembolic pulmonary hypertension, PTS= post thrombotic syndrome, PE=pulmonary embolism, VTE=venous thromboembolism

Results of the sensitivity analyses

Extending the base case results to 2 years, incremental QALYs from enoxaparin versus aspirin were 0.002 (95%CI -0.006, 0.010; p=0.653) and incremental costs reduced to $32 but were imprecisely measured (95%CI -$610, $698, p=0.097). We can be 63% confident that the incremental cost per QALY does not exceed the chosen threshold of $70,000 (Figure A3.3). If PE patients all accrued a cost of hospital stay then, we can be 70% confident that the incremental cost per QALY does not exceed willingness-to-pay threshold of $70,000

(Figure A3.2.b), or 61% confident for a willingness-to-pay of at least $3,850 per VTE avoided (Figure A3.2.1).

The results at 2 years were conservative as there is a small differential effect that favours enoxaparin suggesting that extrapolation beyond the trial for any period favours enoxaparin. All models that show an advantage to a treatment at 12 months show a greater benefit over a lifetime[3,5,6].

Table A3.2. Results of the sensitivity analyses

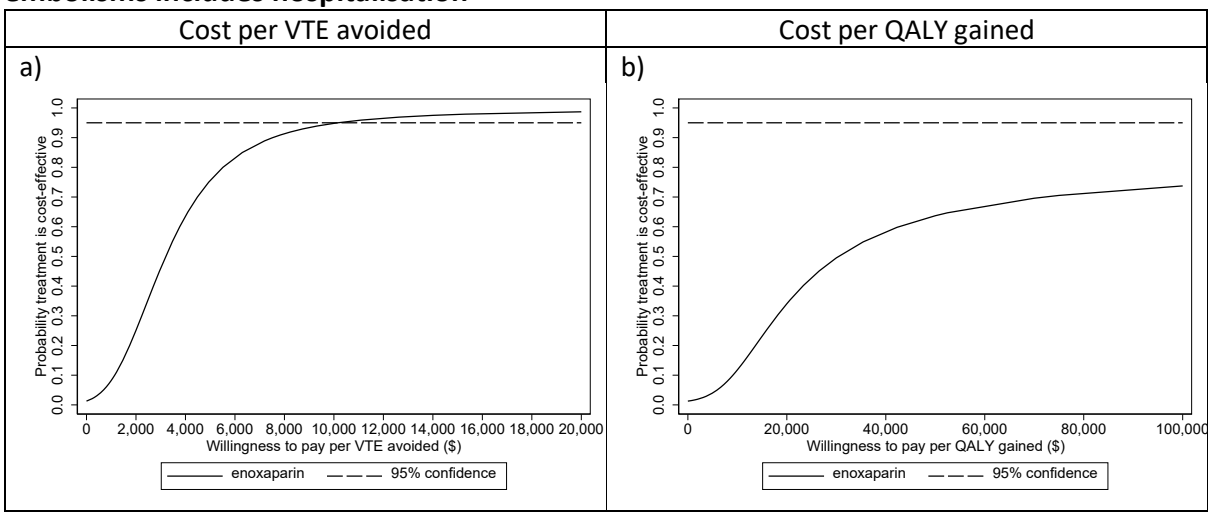
	Incremental enoxaparin versus aspirin (sd)			ICER (95% CI)		Threshold willingness-to-pay for 95% confidence of enoxaparin**	
Sensitivity analysis	Costs	VTE occurrence	QALYs	Per VTE avoided	Per QALY gained	per VTE avoided	per QALY gained
Base case	$82.75 ($7.10)	-0.016 (0.005)	0.002 (0.002)	$5,319 ($3,008, $15,931)	$50,567 ($15,513, dominated)	$12,027	NE
Cost for PE includes hospitalisation	$49.81 ($21.18)	-0.016 (0.005)	0.002 (0.002)	$3,201 ($314, $14,007)	$30,435 ($3,093, Dominated)	$10,159	NE
Extension to 2 years	$31.62 ($18.48)	-0.016* (0.005)	0.002 (0.004)	$2,032* (dominates, $8,376)	$17,977 (dominates to dominated)	$6,263*	NE

VTE=venous thromboembolism, INMB=incremental net benefit, ICER=incremental cost effectiveness ratio, WTP=willingness-to-pay, NE=not estimable (we can never be 95% confident that enoxaparin results in QALY gains at any cost), QALY=quality adjusted life year

*this only considers VTEs avoided within the 90 days of the trial. Recurrent VTEs are captured in the costs, but not the VTEs avoided.

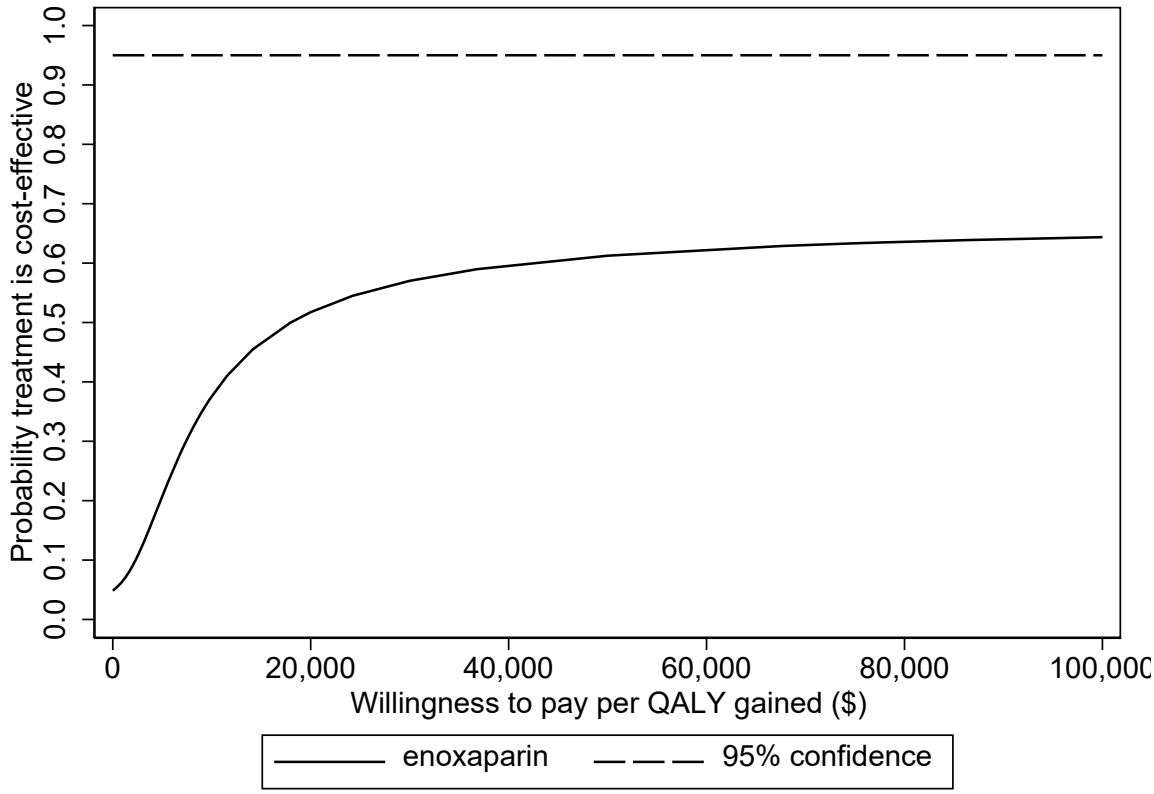
**There is 95% confidence that the incremental cost per outcome (VTE avoided or per QALY gained) of enoxaparin compared to aspirin does not exceed these thresholds willingness-to-pay (i.e. these are the threshold value to achieve one sided p= 0.05).

Figure A3.2. Cost-effectiveness acceptability curves when cost for all pulmonary embolisms includes hospitalisation



VTE=venous thromboembolism, QALY=quality adjusted life year

Figure A3.3. Cost-effectiveness acceptability curves for enoxaparin at 2 years (cost per QALY gained)



QALY=quality adjusted life year

Appendix 4: Alternative statistical model specification

As a sensitivity analysis on regression model specification [12] we analysed cluster-level summary measures of costs and VTEs adjusted for the incomplete crossover [12]. This allows for the correlation of patient observations within clusters across time. For hospitals that experienced crossover, a linear regression was fitted to clinical and cost outcome differences accounting for treatment sequence and the treatment effect estimated by the intercept [13] (eqn. 1). Harmonic mean weights of the number of patients in the two periods were used to adjust for unequal numbers of patients in each hospital.

$$d_i = \beta_{XO} + \gamma w_i + \varepsilon_i \text{ where } \varepsilon_i \sim N(0, \sigma^2) \qquad (1)$$

$$\text{with weight of hospital } i \text{ proportional to } \left(\frac{1}{n_{i1}} + \frac{1}{n_{i2}}\right)^{-1} \text{ where } i = \text{hospital},$$

$$d_i = \text{difference in outcome per patient for hospital } i, \beta_{XO} = \text{treatment effect for crossover},$$

$$n_{ij} = \text{number of patients at hospital } i \text{ in period } j = \{1,2\}, \sigma^2 = \text{variance}$$

For hospitals which did not cross over, a linear regression was conducted with treatment as the only independent variable, (eqn. 2) and the predicted cost was weighted by numbers of patients in each hospital.

$$y_m = \alpha + \beta_P x_m + \epsilon_m \text{ where } \epsilon_{\mathrm{m}} \sim N(0, s^2) \qquad (2)$$

$$\text{with weight of hospital } m \text{ proportional to } \eta_{\mathrm{m}} = \text{number of patients at hospital } m,$$

$$\text{where } y_m = \text{outcome for hospital } m,$$

$$\beta_P = \text{treatment effect for parallel hospitals (i. e. no crossover)},$$

$$\epsilon_{\mathrm{m}} = \text{error for each hospital}, s^2 = \text{variance}$$

Absolute risk differences and 95% confidence intervals were then estimated by combining the crossover and parallel estimates using inverse variance weights.

$$\beta = \frac{\frac{1}{SE_{\beta_{XO}}^2}\beta_{XO} + \frac{1}{SE_{\beta_P}^2}\beta_P}{\frac{1}{SE_{\beta_{XO}}^2} + \frac{1}{SE_{\beta_P}^2}} \quad SE_\beta = \left(\frac{1}{\frac{1}{SE_{\beta_{XO}}^2} + \frac{1}{SE_{\beta_P}^2}}\right)^{\frac{1}{2}}$$

Net monetary benefit was modelled as per the trial-based analysis. All analyses were performed using StataMP version 17 (StataCorp LLC) and R (R Foundation for Statistical Computing Platform) version 4.1.3.

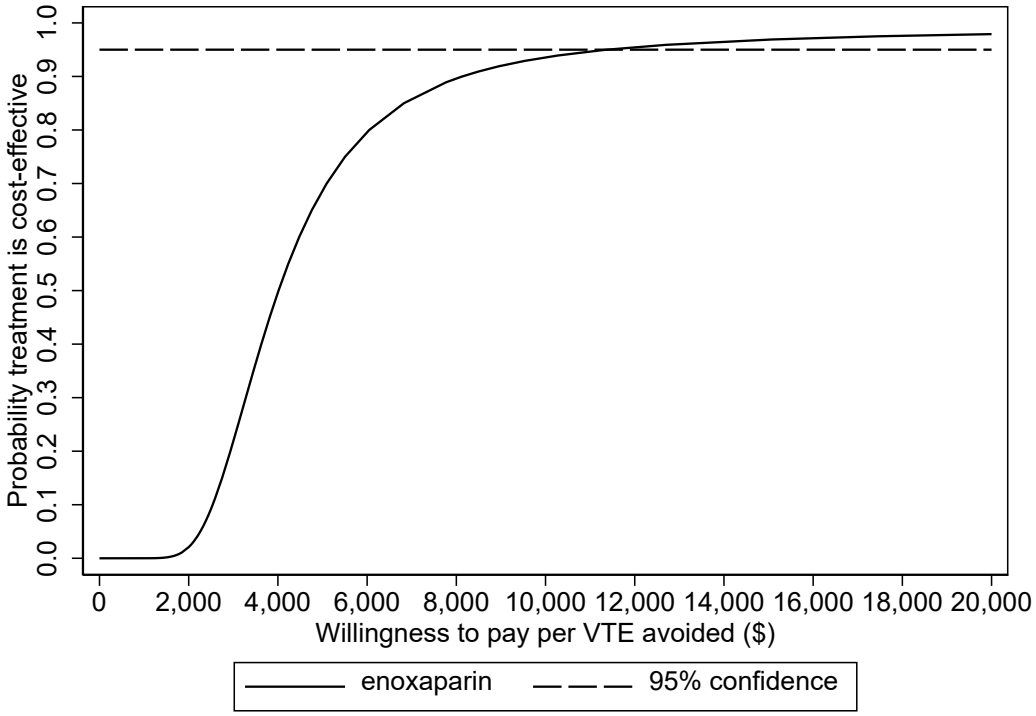
Table A4. Results of the alternate analysis specification based in CRISTAL trial

Cost per patient	Enoxaparin (observed)	Aspirin (observed)	Incremental (95% CI)
VTE prevention	$96.65	$2.55	$92.34 ($88.84, $95.84)
VTE treatment	$4.93	$9.39	-$4.93 (-$9.35, -$0.50)
Bleed complication	$11.37	$13.78	-$7.60 (-$23.77, $8.57)
Total cost[a]	**$113.07**	**$26.11**	**$79.08 ($61.99, $96.18)**
VTE	0.0182	0.0345	-0.0197 (-0.0341, -0.0054)
Cost per VTE avoided			**$4,014 ($2,049, $17,472)**

CI=confidence interval, VTE=venous thromboembolism
a missing data imputed from average cost for bleed complications by treatment arm

A cost effectiveness acceptability curve based on the alternate specification is presented in Figure 3.

Figure A4. Cost-effectiveness acceptability curve for enoxaparin, alternative statistical model specification



VTE=venous thromboembolism

Based on the alternate statistical model specification, we can be 95% confident that the incremental cost per VTE avoided for enoxaparin compared to aspirin does not exceed a willingness-to-pay threshold of $11,379, slightly less than in the main trial-based analysis ($12,027). We cannot be confident that the incremental cost per VTE avoided for enoxaparin compared to aspirin does not exceed the proposed threshold of $3,850 per VTE avoided.

Incremental costs as modelled with alternative GLMs

Alternative generalized linear models were explored to assess the effect of skewness of the costs on the results: including a Gaussian distribution with log link and gamma distribution with log link. All models estimated the incremental cost of enoxaparin compared to aspirin to be $83 (95%CI $68, $97). Therefore, as the results were robust to GLM specification, linear regressions were retained as the base case.

Appendices references

1. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. John Wiley & Sons, Inc.; 1987.
2. The Independent Hospital Pricing Authority. National Efficient Price Determination 2021–22. Accessed 13 February, 2022. https://www.ihacpa.gov.au/resources/national-efficient-price-determination-2021-22
3. Dawoud DM, Wonderling D, Glen J, et al. Cost-Utility Analysis of Venous Thromboembolism Prophylaxis Strategies for People Undergoing Elective Total Hip and Total Knee Replacement Surgeries in the English National Health Service. *Front Pharmacol*. 2018;9:1370-1370. doi:10.3389/fphar.2018.01370
4. National Guideline C. National Institute for Health and Care Excellence: Guidelines. *Venous thromboembolism in over 16s: Reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism*. National Institute for Health and Care Excellence (NICE)

Copyright © NICE 2018.; 2018.
5. Smith SR, Katz JN, Losina E. Cost-Effectiveness of Alternative Anticoagulation Strategies for Postoperative Management of Total Knee Arthroplasty Patients. *Arthritis Care Res (Hoboken)*. Dec 2019;71(12):1621-1629. doi:10.1002/acr.23803
6. Torrejon Torres R, Saunders R, Ho KM. A comparative cost-effectiveness analysis of mechanical and pharmacological VTE prophylaxis after lower limb arthroplasty in Australia. *J Orthop Surg Res*. 2019;14(1):93-93. doi:10.1186/s13018-019-1124-y
7. Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv*. Oct 13 2020;4(19):4693-4738. doi:10.1182/bloodadvances.2020001830
8. Kahn SR, Shbaklo H, Lamping DL, et al. Determinants of health-related quality of life during the 2 years following deep vein thrombosis. *J Thromb Haemost*. Jul 2008;6(7):1105-12. doi:10.1111/j.1538-7836.2008.03002.x
9. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health*. Aug 2010;13(5):509-18. doi:10.1111/j.1524-4733.2010.00700.x
10. Australian Government Department of Health and Aged Care. Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (PBAC) Version 5.0. Commonwealth of Australia; 2016:chap Section 3A Cost-effectiveness analysis.
11. Caprini JA, Botteman MF, Stephens JM, et al. Economic burden of long-term complications of deep vein thrombosis after total hip replacement surgery in the United States. *Value Health*. Jan-Feb 2003;6(1):59-74. doi:10.1046/j.1524-4733.2003.00204.x
12. Sidhu VS, Kelly TL, Pratt N, et al. CRISTAL (a cluster-randomised, crossover, non-inferiority trial of aspirin compared to low molecular weight heparin for venous thromboembolism prophylaxis in hip or knee arthroplasty, a registry nested study): statistical analysis plan. *Trials*. Aug 24 2021;22(1):564. doi:10.1186/s13063-021-05486-0
13. Turner RM, White IR, Croudace T, Group PIPS. Analysis of cluster randomized cross-over trial data: a comparison of methods. *Stat Med*. Jan 30 2007;26(2):274-89. doi:10.1002/sim.2537