**Abstract**

***Objective***

To assess the efficacy and safety of venous thromboembolism (VTE) prophylaxis in people undergoing elective total hip replacement (eTHR).

***Methods***

Systematic review and Bayesian network meta-analyses (NMAs) of randomised controlled trials (RCTs) were conducted for three outcomes: deep vein thrombosis (DVT), pulmonary embolism (PE) and major bleeding (MB). Medline, EMBASE and Cochrane Library (CENTRAL) databases were searched. Study quality was assessed using Cochrane risk-of-bias checklist. Fixed and random effects models were fitted and compared. The median relative risk (RR) and odds ratio (OR) compared to no prophylaxis, with their (95% credible intervals [CrIs]), rank and probability of being the best were calculated.

***Results***

Forty-two (n=24,374, 26 interventions), 30 (n=28,842, 23 interventions) and 24 (n=31,792, 15 interventions) RCTs were included in the DVT, PE and MB; networks; respectively. Rivaroxaban had the highest probability of being the most effective intervention for DVT (RR = 0.06 [0.01 to 0.29]). Strategy of low-molecular-weight-heparin (LMWH) followed by aspirin had the highest probability of reducing risk of PE and MB (RR= 0.0011 [0.00 to 0.096] and OR = 0.37 [0.00 to 26.96], respectively). The ranking of efficacy estimates across the three networks, particularly PE and MB, had very wide CrIs; indicating high degree of uncertainty.

***Conclusions***

A strategy of LMWH given for 10 days followed by aspirin for 28 days had the best benefit-risk balance, with the highest probability of being the best based on the results of the PE and MB NMAs. However, there is considerable uncertainty around the median ranks of the interventions. **Highlights**

***What is already known about this topic?***

1. Previously published systematic reviews have shown that pharmacological and mechanical interventions can be effective in improving VTE-related outcomes in people undergoing elective hip replacement surgery.
2. There is uncertainty about the use of combination VTE prophylaxis strategies with pharmacological and/or mechanical interventions.
3. There is uncertainty about the optimal duration for VTE prophylaxis strategies for people undergoing elective hip replacement surgery.

***What this paper adds to the body of knowledge?***

1. Analyses conducted provide a range of effective VTE prophylaxis strategies that can be used for people undergoing elective hip replacement surgery taking into consideration the outcomes of DVT (symptomatic and asymptomatic), PE and major bleeding.
2. LMWH (standard dose and standard duration) followed by aspirin (low dose for an extended duration) has the highest probability of being a clinically effective VTE prophylaxis strategy, achieving a reduction in PE for people undergoing elective hip replacement surgery.
3. The resulting relative efficacy estimates can be used in economic models to assess the cost effectiveness of these regimens.

***What insights does the paper provide for informing health care-related decision making?***

1. The choice of a VTE prophylaxis strategy requires a trade-off to be made between efficacy and safety, particularly for pharmacological prophylaxis options.
2. A range of VTE prophylaxis options are available and the choice of one over the other requires consideration of not only the benefit-risk balance but also cost effectiveness and patient preferences.

**Introduction**

Hospital-acquired venous thromboembolism (VTE), which includes deep-vein thrombosis (DVT) and pulmonary embolism (PE), is defined as VTE events occurring within 90 days after a hospital admission (1). PE has been highlighted as a potential cause of in-hospital and post-discharge mortality, representing a threat to patient safety (2). There are numerous risk factors associated with developing hospital-acquired VTE including immobilisation, dehydration and older age (3). Undergoing a major orthopaedic surgery such as elective total hip replacement (eTHR) has also been identified as a risk factor for developing hospital-acquired VTE (4).

It has been reported that VTE is the most frequent cause for hospital readmission after eTHR surgery (5). A considerable economic burden is also associated with hospital-acquired VTE and its long-term sequalae. Moreover, the cost of successful patient claims made against the National Health Service (NHS) in the UK for hospital-acquired VTE was over £10,000,000 in 2014, including claimant and defence legal costs as well as damages paid, of which over 50% were made by surgical patients including those who had major orthopaedic surgeries such as eTHR (6). This has put hospital-acquired VTE prevention efforts high on the agenda of the UK NHS as a major patient safety issue. In 2010, guidance by the National Institute for Health and Care Excellence (NICE) in the UK has recommended the use of a combined prophylaxis strategy with pharmacological and mechanical interventions (3).

Pharmacological interventions include: low-molecular-weight heparin (LMWH), unfractionated heparin (UFH), vitamin K antagonists, fondaparinux sodium and directly-acting oral anticoagulants (DOACS) including apixaban, dabigatran etexilate and rivaroxaban. These interventions may be combined with mechanical interventions such as anti-embolism stockings (AES). Other mechanical interventions include foot impulse devices and intermittent pneumatic compressive devices (3). The duration of interventions can be classified as ‘standard’ (average duration: 7-10 days) or ‘extended’ (average duration: 28-35 days). Historically, it was common for patients to remain in hospital for 7-10 days post-operation. Thus, interventions that were administered after discharge were classified as extended.

Systematic reviews have been conducted to evaluate VTE prophylaxis strategies but the majority focused on pharmacological prophylaxis strategies (7) (8) (9) (10). Hence, a systematic review (SR) and network meta-analyses (NMAs) of randomised controlled trials (RCTs) were undertaken to assess the efficacy and safety of the different strategies as single agents or in combination in patients undergoing eTHR surgery to include both pharmacological and mechanical strategies. The aim was to inform the National Institute for Health and Care Excellence (NICE) recommendation regarding VTE prophylaxis in this population in its guideline NG89, (11) updating the recommendations made in its 2010 clinical guideline for reducing the risk of VTE in patients admitted to hospital (CG92) (3).

**Methods**

The protocol for the SR and NMA was developed by the guideline technical team, consisting of information scientist (JC), Research Fellow (SL), Senior Research Fellow (JG) and Senior Health Economist (DD), and approved by the guideline committee (GC) and its orthopaedic subgroup. Members of the GC included haematology specialists, a consultant physician, surgeons, a pharmacist, nurses and two patient members. Members of the orthopaedic subgroup included trauma and orthopaedic surgeons. The protocol followed the PICO format, specifying **P**opulations, **I**nterventions, **C**omparators and **O**utcomes. The protocol, PICO characteristics and outcomes of the complete systematic review are reported in the supplementary material (also available in NG89 Full Guideline (Volume 2) here: <https://www.nice.org.uk/guidance/ng89/evidence/full-guideline-volume-2-pdf-4787002766> ) . No ethics approval was required for this review.

Three outcomes were selected for the NMAs which were deemed as critical for patients undergoing eTHR surgery. Two were measures of efficacy: DVT (both symptomatic and asymptomatic; confirmed by: radioiodine fibrinogen uptake test or venography or duplex (Doppler) ultrasound or magnetic resonance imaging or impedance plethysmography) and PE (confirmed by computed tomography scan with spiral/contrast or pulmonary angiogram or ventilation/perfusion scan including VQSpect or autopsy or echocardiography). One outcome, major bleeding (MB) (defined as one or more of the following criteria: results in death; occurs at a critical site (intracranial, intraspinal, pericardial, intraocular, retroperitoneal); results in the need for a transfusion of at least 2 units of blood; leads to a drop in haemoglobin of ≥2g/dl) was used as a measure of safety. The time-point measurement for the outcomes of DVT and PE was 7-90 days from hospital discharge. The upper-limit of 90 days was set to be in line with the definition of hospital-acquired thrombosis. Similarly, the time-point measurement for MB was set to be up to 45 days from hospital discharge, as this is a drug-related adverse event that can occur only while receiving the pharmacological prophylaxis. Given that the maximum duration for the pharmacological prophylaxis options considered in the review is 35-38 days; it was agreed that bleeding events occurring beyond 45 days are unlikely to be related to the pharmacological prophylaxis.

Searches were run in Medline (OVID), EMBASE (OVID) and the Cochrane Library (Wiley) using population search terms. For Medline and EMBASE, an RCT filter was also added (see supplementary material; part II for the search strategy). As this systematic review was an update of the review conducted for the eTHR population in the CG92 guideline which reviewed studies published between 1950 and the 10th December 2008, the searches were run from 2008 to 19th June 2017. The studies included in CG92 were re-assessed for inclusion. The searches were limited to retrieve material published in English. Reference lists of systematic reviews of RCTs were reviewed for additional trials. Non-RCT study designs, literature reviews and conference abstracts were excluded.

Inclusion criteria for the RCTs were: reporting outcome data that matched time-point measurements (7-90 days or up to 45 days from hospital discharge), assessed doses that were appropriate for current clinical practice in the UK (lower and higher doses were considered if they were within ranges reported in the systematic review protocol (see supplementary material; part III). A random sample of the included studies were checked by a senior reviewer to ensure the appropriateness of the inclusion/exclusion decision (JG).

The following data were extracted from the included studies: study characteristics, sample size, follow-up, interventions and outcomes. Risk of bias was appraised using the NICE risk of bias checklist for RCTs (which aligns with the Cochrane tool) (see supplementary material; part V). No studies were excluded due to high risk of bias, as this would have led to disconnected networks. Outcomes were calculated using the numbers reported by the authors, which was, where possible, on an available case basis. Studies reporting zero events for the outcomes in the intervention/s and comparison arms were excluded from the NMA, as they do not contribute information on relative treatment effects. Studies which reported zero events in one of the intervention/s or comparison arms were included in the NMAs. Zero event cells were treated with the addition of 0.5 to each arm and addition of 1 to the number of participants in each arm. For the MB network, trial arms that evaluated mechanical interventions were deemed as equivalent to no prophylaxis as the assumption was made that these interventions do not influence bleeding risk (12). Data extraction was quality assured by a senior reviewer (JG).

Direct pairwise meta-analyses were conducted in Review Manager Software (RevMan) version 5.3 and results were qualitatively compared to the NMA results*.* Bayesian NMAs were performed using the software WinBUGS version 1.4.3. We fitted both fixed and random effects models to the data and compared their fit. Baseline risk was independently modelled. We adapted a three-arm random effects model template for the networks, from the NICE Decision Support Unit (13). This model accounts for the correlation between study level effects induced by multi-arm trials. The model used was a logistic regression model, with parameters estimated by Markov chain Monte Carlo simulation. As it was a Bayesian analysis, for each parameter the evidence distribution is weighted by a distribution of prior beliefs. Due to the sparse nature of the networks (few studies per direct treatment comparison), the between-study heterogeneity parameter is imprecisely estimated in a random effects model. Therefore, it was deemed appropriate to use informative prior distributions for the heterogeneity parameters to avoid unreasonably wide credible intervals. Turner et al (2015) derived a novel set of predictive distributions for the degree of heterogeneity across 80 different settings (14). Appropriate log-normal (LN) predictive distributions for heterogeneity were chosen from Table IV of Turner et al (2015) according to the outcome and treatment comparison and used as informative priors (14). For the DVT and PE NMAs the distributions defined by the outcome of “general physical health indicators” and by the intervention/comparison type “non-pharmacological vs. pharmacological” were chosen (LN[-1.26, 1.252]). For the MB NMA the distributions defined by the outcome of “adverse events” and by the intervention/comparison type “non-pharmacological vs. pharmacological” were chosen (LN[-0.84, 1.242]). These distributions were chosen as they represented outcomes measured by an assessor, whose method of measurement as well as judgement may influence the outcome (as studies provided slightly variable ways of defining these critical outcomes), and the interaction aspect encompassed both the pharmacological and mechanical prophylaxis options covered in our review protocol.

For both analyses, a series of 60,000 burn-in simulations were run to allow convergence and then a further 60,000 simulations were run on three chains to produce the outputs. Convergence was assessed by examining the history, kernel density plots, and Brooks-Gelman Rubin plots. Goodness of fit of the model was tested by calculating the posterior mean of the residual deviance (13). Both fixed effect (FE) and random effects (RE) models were fitted and compared using the Deviance Information Criterion (DIC) (15) . A lower DIC indicates the model with the best trade-off between complexity and fit, with a difference of 3 to 5 considered important.

We tested for inconsistency by fitting inconsistency models using code from Dias et al. (13). We compared the posterior mean of the residual deviance between the consistency and inconsistency models to see which model was a better fit to the data (closest to the number of trial arms in each network). We also checked if the difference in DIC values between the two models was small (less than a difference of 3 to 5) or if it was large (more than a difference of 5). If there was a smaller DIC for the consistency models, no significant inconsistency was evident. We also examined the auto-correlation plots to confirm the absence of auto-correlation. The MC error was cheked to ensure that it was less than 5% of the standard deviation for the parameters. No thinning was applied.

Results were presented as rankings for interventions, according to their relative effect compared to the control (reference) intervention. Relative effects obtained from the NMA are reported as medians (with 95% CrI). For DVT and PE, we used data on the baseline risks of these outcomes from a published UK observational cohort study of data from the National Joint Registry for people undergoing eTHR who received LMWH (standard dose, standard duration)+ AES for VTE prophylaxis (16). This data was used to model baseline risk as a binomial distribution which was used in the main NMA model to calculate the relative risks (RRs) and their 95% CrIs. For MB, we did not have data for the baseline risk of all MB from the same study, so we report the results as ORs instead. The median ranks for all the interventions are presented on a rank plot with the associated 95% credible intervals (CrI).

**Results**

The search retrieved 8994 articles, 926 of these were assessed for eligibility and 50 papers met the inclusion criteria and were included in the systematic review (see supplementary material; part IV).

The characteristics of these studies are summarised in Table 1. See Figure 1 for the DVT network diagram and supplementary material part VI for the network diagrams for the PE and MB outcomes and the full extracted data.

**Insert table 1**

**Insert Figure 1**

Forty-four studies were included across the 3 NMAs (excluding papers that reported zero events in each arm and papers reporting on combinations that did not connect to any other intervention in the network) (see Table 1). Nine studies had very high risk of bias, 26 studies had high risk of bias and 9 studies had low risk of bias. The main contributing bias factors were due to selection bias, performance bias and attrition bias (see supplementary material; part V). The evidence for each outcome (DVT, PE and MB) also ranged from very low to high risk of bias (for further details see Full Volume 2; NG89 (11)).

***Efficacy outcomes:***

***DVT (symptomatic and asymptomatic)***

After considering the exclusion of papers that reported zero events in each arm and papers reporting on combinations that did not connect to any other intervention in the network all 42 trials (n=24,374), published in 41 papers and involving 26 interventions were included in the DVT network as none of the studies reported zero events and all connected to the network (see Figure 1). The study data are presented in the supplementary material, Part VI.

When both the FE and RE models were fitted, the RE model had a DIC of 570, lower than that of the FE model which had a DIC of 634. Examining the history, kernel density plots, and Brooks-Gelman Rubin plots confirmed convergence (see supplementary material, part IX). The RE model used is a good fit, with a residual deviance of 90. This corresponds well to the total number of trial arms, 88. The between trial standard deviation in the random effects analysis was 0.78 [0.52 to 1.16].

The highest-ranking interventions were rivaroxaban (RR=0.06 [0.01 to 0.29]), followed by fondaparinux in combination with AES (RR=0.07 [0.01 to 0.49]), then LMWH at a standard dose for an extended duration in combination with AES (RR=0.08 [0.01 to 0.61]). As expected, “no prophylaxis” was the lowest ranked strategy. The full ranking of the interventions is presented in Figure 2. The ranking probability matrix plots for all interventions are included in the supplementary material, appendix IX.

The results for the pairwise meta-analysis results versus the NMA results for the interventions compared with no prophylaxis can be seen in Table 2 (see also supplementary material; part VII)

**Insert Figure 2 here**

**Insert Table 2 here**

***PE***

Thirty studies (n=28,842) involving 23 interventions were included in the PE network (see supplementary material, Part VI), including 15 studies which reported zero events in one arm. Seven studies were excluded due to the reporting of zero events in both arms. The included study data are presented in the supplementary material, Part VI.

The RE model had a DIC of 255 compared with 276 for the FE model. Examining the history, kernel density plots, and Brooks-Gelman Rubin plots confirmed convergence (see supplementary material, part IX). The model was a good fit, with a residual deviance of 61 reported. This corresponds well to the total number of trial arms, 62. The between-trial standard deviation was 0.41 [0.14 to 1.04].

The highest-ranking interventions were LMWH at standard dose for 10 days followed by aspirin low dose for 28 days (RR=0.0011 [0.00 to 0.096]) followed by LMWH at a high dose for an extended duration (RR=0.0024 [0.00 to 0.81]) and LMWH at a high dose for a standard duration in combination with AES (RR=0.0049 [0.00 to 0.30]) (see Figure 2). LMWH at a standard dose for a standard duration followed by aspirin low dose for an extended duration had a median rank of 2.0 [1 to 9]. Aspirin low dose for a standard duration had the lowest median rank 22.0 [10 to 23], while no prophylaxis had a median rank of 20.0 [14 to 23].

The results for the pairwise meta-analysis results versus the NMA results for the interventions compared with no prophylaxis can be seen in Table 3 (see also supplementary material; part VII). The full ranking of the interventions is presented in the supplementary material, Part VI. The ranking probability matrix plots for all interventions are included in the supplementary material, part IX.

**Insert Table 3 here**

***Safety Outcome:***

***MB***

Twenty-four studies (n=31,792) involving 15 interventions were included in the MB network (see Figure 1), including 8 studies which reported zero events in one arm. Four studies were excluded from the network as they reported zero events in both arms. The included study data are presented in the supplementary material, Part VI.

The RE model had a DIC of 275 compared with 276 for the FE model. Examining the history, kernel density plots, and Brooks-Gelman Rubin plots confirmed convergence (see supplementary material, part IX). Given the clear heterogeneity in the evidence, which was evident from the DVT and PE networks, the RE model was used. It had a good fit, with a residual deviance of 55. This corresponds well to the total number of trial arms, 51. The between trial standard deviation in the RE analysis was 0.56 [0.19 to 1.27].

The highest-ranking interventions included LMWH at a standard dose for 10 days followed by aspirin low dose for 28 days (OR= 0.37 [0.00 to 26.96]), no prophylaxis/mechanical prophylaxis (reference treatment) and VKA for a standard duration (OR= 1.54 [0.31 to 7.94]) (see Figure 2). The median rank for the top intervention was 1.0 [1 to 15], no prophylaxis the next best ranked prophylaxis strategy had a median rank of 3.0 [1 to 10]. The lowest ranked interventions were VKA for an extended duration (OR= 8.21 [0.13 to 7883.00]), fondaparinux (OR= 4.28 [1.07 to 18.66]) and dabigatran (OR= 3.63 [0.74 to 18.48]).

The pairwise meta-analysis and the NMA results for the interventions compared with no prophylaxis can be seen in Table 4 (see also supplementary material; part VII). The full ranking of the interventions is presented in the supplementary material, Part VI. The ranking probability matrix plots for all interventions are included in the supplementary material, part IX.

**Insert Table 4 here**

**Discussion**

To our knowledge, this is the most up-to-date and comprehensive review and meta-analysis of VTE prophylaxis strategies’ in terms of efficacy and safety following eTHR. It is the first systematic review and NMA that compared all relevant prophylaxis strategies including pharmacological, mechanical and combinations of both. Additionally, it is one of few analyses that considered the different doses and durations of prophylaxis strategies; taking into account the dose-response relationship of these agents (61-63,64).

Our review identified 50 RCTs. We combined the effect estimates in three NMAs for the critical outcomes; namely: DVT (symptomatic and asymptomatic), PE and MB. Although, it might be argued that symptomatic VTE events are the most clinically relevant, focusing on symptomatic events ignores the potential transformation of asymptomatic DVT to symptomatic DVT and PE as well as the potential long-term complications of these asymptomatic events, such as the development of post-thrombotic syndrome (PTS). Given the low incidence of symptomatic DVT; focusing only on the symptomatic events results in imprecise estimates of relative efficacy (3)(61).

In the DVT network, the top three interventions in terms of prevention of DVT were rivaroxaban, fondaparinux plus AES and LMWH (standard dose, extended duration) plus AES. The bottom three interventions were no prophylaxis, UFH (extended duration) and IPCD (length unspecified). These results are in line with earlier reviews that reported the efficacy of pharmacological prophylaxis options; with rivaroxaban showing superiority in terms of DVT prevention in the eTHR population (61).

In the PE network, the top intervention was the combination of LMWH (standard dose, standard duration) followed by aspirin (low dose, extended duration). The second and third ranked strategies were LMWH (high dose, extended duration) and LMWH (high dose, standard duration) plus AES. The bottom three interventions were aspirin (low dose, standard duration), foot pump and no prophylaxis. The top-ranking intervention LMWH (standard dose) for 10 days followed by aspirin (low dose) for 28 days represented a novel approach, where the use of aspirin as a follow-on prophylaxis reduces the need for continuing the parenterally-administered LMWH beyond discharge. This is likely to improve patient convenience and adherence and reduce the costs required for nurse administration. It is also likely to reduce the incidence MB associated with the use of more potent pharmacological prophylaxis for longer durations. This approach has been recently used in another RCT that assessed the efficacy of rivaroxaban for 5 days followed by aspirin for 30 days compared to rivaroxaban for its licensed duration of 35 days (65). The results of both the DVT and PE analyses suggested that combination strategies and those used for extended durations are likely to be more effective compared to strategies used for shorter duration and those consisting of a single mechanical prophylaxis method, with IPCD and foot pump ranking among the three worst interventions in the DVT and the PE NMAs, respectively. This result was in line with current practice, where mechanical interventions are usually recommended for people with low risk of VTE (3).

Overall, the results of the DVT and the PE NMAs were largely aligned. However, there was more uncertainty regarding the ranking of the individual strategies in the PE NMA, with very wide and overlapping credible intervals. This is due to the sparse nature of the network, with small number of events and RCTs for each pairwise comparison. This was in line with previous NMAs in this area (3)(61). Studies were excluded from the PE network and MB network due to reported of zero events in both arms; this has also contributed to the sparsity in the networks.

The MB network results showed the superiority of the low intensity, shorter duration strategies while those with higher doses and/or longer duration ranked much lower. Surprisingly, however, the highest ranked intervention was the combined strategy of using LMWH (standard dose, standard-duration) followed by aspirin (low dose, extended duration); despite this being the top ranked strategy in terms of PE prevention. This was followed by no prophylaxis and VKA at a standard duration. The bottom three interventions were VKA at an extended duration, fondaparinux and dabigatran. Bleeding events following pharmacological prophylaxis use is a current concern among healthcare professionals. Results from the MB network suggest that rivaroxaban might be safer than previously thought in relation to MB. This is in agreement with findings from other recent systematic reviews (61). Similar to the PE network, there was a lot of uncertainty within the MB network with very wide credible intervals for all of the interventions. These very wide credible intervals probably account for the unusual rank of “no prophylaxis” as the second, rather than the best intervention in terms of MB.

In summary, the three outcomes chosen for analysis are the most critical for clinical decision making in terms of assessing clinical efficacy and safety of VTE prophylaxis strategies. Additionally, combining the results of all available RCTs in a pooled analysis which combines direct and indirect evidence increases power and precision of the results. All three network models fit well, as demonstrated by residual deviance statistics. However, there was moderate to high heterogeneity. Additionally, due to the sparse nature of the PE and MB networks, and low event rates, the CrIs around the ranking of treatments in these networks were wide and overlapping. Furthermore, studies with different follow-up periods were combined in the DVT and PE networks (7 to 90 days). The appropriateness of this decision was confirmed with the clinical experts on committee who advised that the majority of the DVT and PE events are expected to occur during the early post-surgical period (i.e. by the shortest follow-up). This decision has been made to maintain an acceptable level of analysis power, particularly in the PE network, given the small number of trials and events and to avoid not including some of the interventions in the analysis if data is available at one follow-up only. This may be seen to affect the interpretation of the results for some comparisons (e.g. comparing the standard and extended duration prophylaxis regimens). However, this is unlikely to be the case here as these interventions have also been assessed in head to head RCTs that were included in the analysis.

Nevertheless, this review and accompanying NMAs provided a hierarchy of the available VTE prophylaxis strategies for the eTHR population, in terms of both efficacy and safety. The results confirm the need for a trade-off to be made between efficacy and safety of the pharmacological prophylaxis interventions, where those with higher efficacy in VTE prevention likely to be associated with higher risk of bleeding. Thus, clinicians need to consider this benefit-risk balance when making their prescribing decisions.

In this analysis, the top-ranking intervention, in terms of efficacy (PE) and safety (MB), was LMWH (standard dose, standard-duration) followed by aspirin (low dose, extended duration). This is a strategy that also has a cost advantage compared to LMWH (standard dose, extended duration) +AES, being much cheaper. This economic advantage can encourage the adoption of this new regimen in clinical practice. Additionally, switching to an orally administered option (aspirin) in the post-discharge phase of treatment is likely to be preferable for patients and clinicians due to ease of administration.

A full economic evaluation undertaken based on this analysis during the guideline development confirmed that LMWH (standard dose, standard-duration) followed by aspirin (low dose, extended duration) is the most cost-effective option (66). This review and NMAs, together with the accompanying economic evaluation, directly informed the NICE guideline committee’s decision to recommend the use of this regimen as the first option for VTE prophylaxis in people admitted for eTHR in all English NHS hospitals (11).

**Conclusion**

The SR and NMAs presented in this publication provide a comprehensive summary of the current evidence base for pharmacological and mechanical strategies used for preventing hospital-acquired VTE in people admitted for elective total hip replacement. The results show that LMWH (standard dose) given for 10 days followed by aspirin (low dose) for 28 days is the preferred strategy in terms of PE prevention and incidence of MB. Rivaroxaban, however, was found to be the most effective for prevention of DVT. The choice between these strategies requires assessing their cost effectiveness in a country-specific economic evaluation.

**Author contributions**

SL completed the SR, conducted NMAs and drafted the manuscript. JG undertook quality assurance of data extractions and conducted NMAs. DD contributed to developing the review protocol, conducting the NMAs and drafting the manuscript. JC conducted the database searches. SD provided support and advice on the NMA models. XG, CS, GS and PB contributed to the design of the study, acquisition of the data and the interpretation of the results. The manuscript was revised by all authors and the submission of the final manuscript was approved by all authors.

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**Figures**

**Figure 1: Network diagram for the outcome DVT (symptomatic and asymptomatic)**

**Figure 2: Rank-O-gram for the outcome DVT (symptomatic and asymptomatic)**

**Tables**

**Table 1: Study characteristics for included studies**

**Table 2: Relative risk for DVT (symptomatic and asymptomatic), interventions compared with the reference treatment (no prophylaxis)**

**Table 3: Relative risks for PE, interventions compared with the reference treatment (no prophylaxis)**

**Table 4: Odd ratios for major bleeding, interventions compared with the reference treatment (no prophylaxis)**