Title (full): Venous thromboembolism prophylaxis strategies for people undergoing elective total knee replacement: a systematic review and network meta-analysis

Title (descriptor): Thromboembolism prophylaxis in total knee replacement: systematic review and network meta-analysis

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Summary

Background

Hospital-associated venous thromboembolism (VTE) is a major patient safety concern. Provision of prophylaxis to people admitted for elective total knee replacement (eTKR) has been proposed as an effective strategy to reduce VTE events. The aim of this study was to assess the relative efficacy and safety of available VTE prophylaxis strategies.

Methods

Systematic review and network meta-analyses of randomised controlled trials were conducted to assess the relative efficacy and safety of VTE prophylaxis strategies to populate an economic model that assessed the cost effectiveness of these strategies and informed NICE guideline recommendation for the eTKR surgery population in the updated guideline, NG89. Cochrane Library (CENTRAL), EMBASE and Medline were last searched on 19 June 2017 using the key terms relating to the population (VTE and TKR) and the interventions compared. The outcomes were: deep vein

thrombosis (DVT) (symptomatic and asymptomatic), pulmonary embolism (PE) and major bleeding (MB). Risk of bias was assessed, and data extracted for the network meta-analyses. Relative risks compared to no prophylaxis, ranks and probability of being the best were calculated. The study was undertaken in accordance with PRISMA guidelines.

Findings

Twenty-three trials (19 interventions; n=15,028) were included in the DVT, 12 in the PE (13 interventions; n=15,555) and 19 in the MB (11 interventions; n=19,797) networks. Risk of bias ranged from very low to high. Rivaroxaban ranked first for DVT prevention (RR=0.12 [0.06 to 0.22]). Low-molecular-weight-heparin (LMWH) (standard prophylactic dose, for 28-35 days) ranked first in the PE network (RR = 0.02 [0.00 to 3.86]) and LMWH (low prophylactic dose for 14 days) ranked first in the MB network (OR = 0.08 [0.00 to 1.76]) but the results for PE and MB are highly uncertain.

Interpretation

Single VTE prophylaxis strategies are more effective in prevention of DVT, in the eTKR population, than combination strategies with rivaroxaban being the most effective. The results of the PE and MB meta-analyses are uncertain and no clear conclusion can be made other than what is biologically plausible.

Funding

The National Institute for Health and Care Excellence (NICE).

Introduction

Hospital-acquired venous thromboembolism (VTE) is a major patient safety concern.(1, 2) It is defined as any deep-vein thrombosis (DVT) or pulmonary thromboembolism (PE) events that occur during or within 90 days after a hospital admission.(3) It is estimated that the costs associated with hospital-acquired thromboembolism (HAT) in the UK in 2016-2017 was on average around £940,000 per clinical commissioning group (CCG), taking into account the cost of treatment, hospital bed days, sanctions and litigation.(1) People undergoing major orthopaedic surgery, particularly elective total hip replacement (eTHR) and elective total knee replacement (eTKR), are at increased risk of developing VTE, with an incidence of >50% taking into account both symptomatic and asymptomatic events. (3)

Given this high disease burden, effective prophylaxis strategies in the eTKR surgery population have been extensively investigated. In 2010, the National Institute for Health and Clinical Excellence (NICE) recommended the use of combination prophylaxis strategies with pharmacological and mechanical interventions for a duration of 10 to 14 days.(4) Mechanical interventions were recommended to start on admission with a choice from anti-embolism stockings (AES), foot impulse devices, and intermittent pneumatic compression devices (IPCD). One of the following pharmacological interventions was recommended to be added after surgery: dabigatran, fondaparinux sodium, low-molecular-weight-heparin (LMWH) or unfractionated heparin (UFH).(4) The American College of Chest Physicians (ACCP) recommends similar pharmacological interventions (as well as aspirin) or IPCD as an individual prophylactic agent for eTKR surgery.(5) Previous systematic reviews and meta-analyses have either mainly focused on evaluating the use of pharmacological interventions, with particular focus on the new direct-acting oral anticoagulants (DOACs), included a smaller number of interventions or combined eTKR with elective total hip replacement population.(6-12)

As part of updating NICE guideline CG92, this systematic review and Bayesian network meta-analyses of randomised controlled trials (RCTs) were undertaken to assess the relative efficacy and safety of the VTE prophylaxis strategies (pharmacological, mechanical and combinations of both) in the eTKR surgery population. The literature was searched to identify all published relevant trials indexed in databases up to 19 June 2017. This search cut-off date was decided to allow enough time for all relevant trials published up to this date to be included in the updated guideline published in March 2018. The results of this review and network meta-analyses were also required to populate an economic model that assessed the cost effectiveness of these strategies and informed the guideline recommendation for the eTKR surgery population in the updated guideline, NG89.(13) Here, we report on this systematic review and network meta-analyses.

Methods

The review protocol detailing the **P**opulation, **I**ntervention, **C**omparator and **O**utcomes (PICO) was developed by the guideline technical team (SL, JG, DD, JC) in line with the NICE Guideline Manual with input from the guideline committee (GC) and its orthopaedic subgroup (members included

trauma & orthopaedic surgeons and patient representative).(14) The GC included general surgeons, a pharmacist, haematologists, nurses, a consultant physician and two patient representatives.

Study design and population

The review protocol including the PICO characteristics is reported in the appendix (page 11-12). The population was defined as "adults and young people (16 years and older) undergoing elective knee replacement admitted to and discharged from hospital". To be included, a study had to be a randomised controlled trial comparing two or more of the VTE prophylaxis intervention of interest (see appendix, page 11-12 for a full list of interventions). Non-RCT study designs were excluded, in accordance with NICE guideline development methods, given the availability of RCTs that are relevant for this review. Conference abstracts were also excluded.

Procedures

Searches were run in EMBASE (OVID), Medline (OVID) and the Cochrane Library (Wiley) (see appendix, pages 3-10 for search strategies). Searches were limited to retrieve RCTs published in English. This systematic review was an update of the review conducted for the CG92 guideline, in which studies published between 1950 and the 10th December 2008 were reviewed. Thus, the updated searches were run from 2008 to 19th June 2017. Studies that were originally included in the CG92 guideline were re-assessed for eligibility in this updated systematic review. Relevant articles identified within the searches from 2008 were also assessed for eligibility according to the protocol (appendix, page 11-12). Forward citation searching was also performed. Trial registries and grey literature were not searched. Inclusion decisions were made by one reviewer (SL) and quality checked by a senior reviewer (JG). Any disagreement was resolved by discussion between the two reviewers and/or input from the guideline committee.

Outcomes

The network meta-analyses were undertaken for three outcomes, deemed critical for decision-making and were required for economic modelling: DVT (both symptomatic and asymptomatic), PE and major bleeding (MB).(15) Data were extracted from the included RCTs that matched time-point measurements. Studies that reported no events in all study arms were excluded from the network meta-analyses, as they do not contribute information on relative treatment effects. In the MB network,

trial arms that evaluated mechanical interventions were deemed as equivalent to no prophylaxis, as it was assumed that these interventions do not influence bleeding risk.(16)

Study characteristics, sample size, follow-up, interventions and outcome data were extracted from the included RCTs and tabulated. Risk of bias was assessed using the NICE risk of bias checklist for RCTs which aligns with the Cochrane risk of bias tool by SL.(17)

Statistical analysis

Direct pairwise meta-analyses were conducted in Review Manager Software version 5.3. Bayesian network meta-analyses were performed using WinBUGS 1.4.3. The model template developed by NICE Decision Support Unit (DSU), which correctly accounts for the correlations in trials with more than 2 arms, was adapted, by including the analysis specific inputs such as number of studies and number of interventions, and used. (18) The method used for the network meta-analyses has been described in more detail elsewhere (Appendix M of NG89).(19)

In summary, 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, we followed recommended practice to use informative prior distributions for the heterogeneity parameters to avoid unreasonably wide credible intervals.(18) Turner et al (2015) derived a novel set of predictive distributions for the degree of heterogeneity across 80 different settings. (20) Appropriate predictive distributions for heterogeneity were chosen from Turner et al (2015) and used as informative priors. (20)

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, auto-correlation and Brooks-Gelman Rubin plots. Goodness of fit of the model was tested by calculating the posterior mean of the residual deviance.(18) Random effects (RE) model was used due to the heterogeneity of the included studies and interventions. The assumption underlying any network meta-analysis is that both direct and indirect evidence are estimating the same relative effect, that is they are consistent. Ensuring

consistency is important to ensure that the model results are credible. We tested for inconsistency by fitting inconsistency models for networks of binary outcomes, as recommended practice, using the NICE DSU code from Dias et al.(18) 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 deviance information criterion (DIC) values between the two models was small (less than a difference of 3-5) or if it was large (more than a difference of 5), chose the model with the lower value. An improvement in model fit or DIC for the inconsistency model would suggest this model better reflects the data, which can be interpreted as evidence of inconsistency.(18)

Relative effects obtained are reported as medians (with 95% credible intervals (CrIs)). For the DVT and PE networks, baseline risk data from a published UK observational cohort study were used to calculate the relative risks (RRs) from the odds ratios (ORs).(18, 21) We used this cohort study as it utilises the best available observational data for the UK cohort of TKR patients from the National Joint Registry (NJR), thus enabling the calculation of absolute event rates for use in the economic model. There was not any appropriate data for the baseline risk of MB from this study; thus, results for the MB analysis are reported as ORs. The median ranks for the interventions in the 3 network meta-analyses are presented in a rank plot with the associated 95% CrIs. No sensitivity analyses were undertaken.

Role of funding source

The funding body (NICE) did not play any direct role in the study design; the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication. The views expressed in this publication are those of the authors and are not necessarily those of the Institute. All researchers involved in this work were independent from the funding body at the time of completing this work. All authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 8994 articles retrieved, 25 RCTs published up to 19 June 2017 were included in the network meta-analyses (see Figure 1 for the search flow chart). (22-46) The characteristics of the included RCTs are summarised in the appendix (pages 13-17, Table 1) and the network diagrams are presented in the appendix (pages 18-19, Figure 1). The extracted outcome data are reported in the appendix (pages 21- 26, Tables 2-4). A list of excluded studies with reasons for exclusion is included in the appendix (pages 37 to 52).

Insert Figure 1 here

The evidence for each outcome (DVT, PE and MB) ranged from very low to high risk of bias (See appendix; page 20 for summary plot). The main contributing factors to the risk of bias were selection bias, performance bias and attrition bias.

Twenty-three studies (n=15,028) involving 19 interventions were included in the DVT network (see appendix, page 11). The RE model had a good fit, with a residual deviance of 51, corresponding well to the total number of trial arms in the network, 51. The between-trial standard deviation was 0.24 (0.09 to 0.56). The DIC for the consistency model was lower than that for the inconsistency model, and hence it was the better fitting model.

The top three interventions in the DVT network were: rivaroxaban (RR=0.12 [0.06 to 0.22]), followed by apixaban (RR=0.15 [0.07 to 0.26]), then LMWH at a high prophylactic dose for a standard duration (10 to 14 days) (RR=0.18 [0.10 to 0.30]). No prophylaxis ranked last (median rank: 19; [15 to 19]). The median ranks of all interventions are presented in Figure 2a.

The results of the pairwise meta-analysis, for all interventions compared to no prophylaxis, and the corresponding network meta-analysis estimates are presented in Table 1. The relative efficacy estimates for all other pairwise comparisons in the network are included in the appendix (pages 27-36).

Insert Figure 2 (a-c) here

Insert Table 1 here

Twelve studies (n=15,555), of 13 interventions, were included in the PE network (see appendix, page 19). The RE model had a DIC of 125 and a residual deviance of 32, corresponding well to the total number of trial arms (28). The between-trial standard deviation was 0.67 (0.18 to 1.98).

The top ranked interventions in terms of median RR were LMWH at standard prophylactic dose for an extended duration (28 to 35 days) (RR=0.02 [0.00 to 3.86]) followed by rivaroxaban (RR=0.08 [0.00 to 6.65]) and IPCD (length unspecified) (RR=0.20 [0.00 to 8.53]) (see Figure 2b). UFH had the lowest median rank (11.0 [2-13]), while no prophylaxis had a median rank of 10.0 [2 to 13].

The results of the pairwise meta-analysis, for all interventions compared to no prophylaxis, and the corresponding network meta-analysis estimates are presented in Table 2. The median ranks of all interventions are presented in Figure 2b.

Insert Table 2 here

Nineteen studies (n=19,797), of 11 interventions, were included in the MB network (see appendix, page 19). The RE model had a DIC of 196 and a residual deviance of 41, corresponding well to the total number of trial arms, 40. The between trial standard deviation was 0.54 (0.19 to 1.28).

The top ranking interventions were: LMWH at a low prophylactic dose for a standard duration (10 to 14 days) (OR= 0.08 [0.00 to 1.76], LMWH at a standard prophylactic dose for an extended duration (28 to 35 days) (OR = 0.21 [0.00 to 10.41]) and Vitamin K antagonists (VKA) (OR= 0.52 [0.08 to 2.89]) (see Figure 2c). The lowest ranked interventions were fondaparinux (median rank: 11 [7 to 11]; OR = 6.74 [0.79 to 76.28]), rivaroxaban (median rank 11 [3 to 11]; OR =1.55 [0.32 to 7.35]) and LMWH at a standard prophylactic dose for a standard duration (10 to 14 days) (median rank: 7 [3 to 10] OR = 1.09 [0.34 to 3.75]).

The results of the pairwise meta-analysis, for all interventions compared to no prophylaxis/mechanical prophylaxis, and the corresponding network meta-analysis estimates are presented in Table 3. The median ranks of all interventions are presented in Figure 2c.

Insert Table 3 here

Discussion

This systematic review identified 25 RCTs that provided outcome data appropriate for three network meta-analyses: DVT (symptomatic and asymptomatic), PE and MB. The results showed that the top-ranking intervention in terms of prevention of DVT was rivaroxaban, while two different LMWH regimens ranked first in terms of PE prevention and incidence of MB. The results of the PE and MB

analyses were highly uncertain due to the sparse nature of the networks and the limited number of RCTs per comparison and no firm conclusions can be made based on the results of these two networks.

To our knowledge, this study presents the most up to date and comprehensive systematic review and network meta-analyses undertaken to assess the efficacy and safety of VTE prophylaxis strategies for the eTKR surgery population. All the included strategies were categorised in terms of doses (differentiating between low, standard and high prophylactic doses for LMWH) and durations. This allowed us to accurately account for the dose-response relationships for the pharmacological interventions which has not been the case in previously published analyses.(12, 47-49)

In this analysis, the DVT outcome data included both symptomatic and asymptomatic events, rather than solely symptomatic events that are often deemed as more clinically relevant. As an outcome, symptomatic DVT is usually reported based on subjective examination by the clinicians and, in patients who have pain and swelling as a result of their surgery, is difficult to detect. In eTKR surgery, where pain and swelling can be a result of the surgical procedure, the differentiation between symptomatic and asymptomatic DVT can be problematical and there is a possibility of under-diagnosis of DVT. In addition, isolated calf vein DVT, whose natural history is uncertain in any event, may be a result of direct surgical trauma and not necessarily reflect any inherent thrombotic tendency. It was important therefore to identify all DVT (symptomatic and asymptomatic). Symptomatic events are also rare and this means the number of events included in the network meta-analysis would be very small, resulting in networks with sparse data and unstable results. Although asymptomatic events are not immediately relevant, clinically, there is a small chance that some of these events can change in the short term to symptomatic DVT or PE and, in the longer term, can lead to post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (CTEPH).(50) These long term effects negatively affect patients' quality of life and are costly events to manage.(50)

Mechanical prophylaxis for the eTKR surgery population is perceived to be less clinically effective compared to pharmacological interventions. However, the DVT network rankings showed the potential efficacy of foot pumps in reducing DVT events, though with a degree of uncertainty. Additionally, ACCP guidance has recommended IPCD as a single prophylactic strategy and suggested that it is a preferable prophylactic strategy for patients who may be concerned about the bleeding risk

associated with pharmacological agents and less concerned about the potential inconvenience of using IPCDs.(5) Hence, mechanical interventions appear to have potential as effective prophylaxis strategies in this population, particularly those who are at risk of MB and hence are unable to use pharmacological prophylaxis.

In the UK, combination prophylaxis strategies consisting of pharmacological and mechanical interventions were recommended for the eTKR surgery population in the CG92 guideline.(51) The results of this updated review and network meta-analyses showed that these combination prophylaxis strategies may not be as effective, as previously thought, in reducing DVT. For example, LMWH (at a standard prophylactic dose for a standard duration) in combination with AES had a RR of 0.42 (0.24 to 1.00) compared to no prophylaxis while LMWH alone at the same dose and duration had better efficacy with RR of 0.26 (0.15 to 0.43) compared to no prophylaxis (see table 2 for more examples) This calls into question the value of combined prophylaxis in this population, which needs to be further examined in head-to-head RCTs.

The use of aspirin for VTE prophylaxis has been associated with contention and much-discussion due to the uncertainty around its efficacy in VTE prevention.(52) However, within the orthopaedic community aspirin has been supported for surgical populations such as the eTKR population.(21) The network meta-analysis conducted for the DVT outcome suggests that aspirin could in fact be effective in reducing DVT, where it ranked better than some LMWH-based strategies. Unfortunately, there were no MB data reported in the aspirin trials to allow its inclusion in the MB network. The availability of such data would enable us to assess the benefit-risk balance of using aspirin as VTE prophylaxis strategy in this population.

DOACs, including rivaroxaban, apixaban and dabigatran, have been recommended by NICE in technology appraisals (TA287, TA327 and TA341) as prophylaxis strategies in the eTKR surgery population.(53-55) For the DVT network, these DOACs have been ranked in the top 10 (in terms of median RR) with rivaroxaban and apixaban ranked as the top 2 strategies with relatively narrow credible intervals, similar to findings from another systematic review.(56) Whilst all the DOACs are deemed to be effective strategies in terms of reducing DVT, rivaroxaban performed slightly better, based on the point estimates, compared to apixaban and dabigatran (RR: 0.12, 0.15 and 0.25 respectively).

Similar to the MB network, there is significant uncertainty in the PE network with the majority of the credible intervals spanning across all of the rank positions. This is consistent with previous network meta-analyses in this area and is a result of the rarity of these events in the included trials.(4, 12) This uncertainty makes it difficult to draw firm conclusions based on the results of these two networks.

Ten pharmacological prophylaxis strategies were assessed for the MB network - for this outcome mechanical prophylaxis strategies were combined with the “no prophylaxis” intervention and treated as equivalent. This is biologically plausible as these strategies are unlikely to affect bleeding. (10)

It was noted that there was variation in the MB definitions used in studies included in the MB network meta-analysis. A majority of the studies reported overlapping definitions including overt bleeding requiring a transfusion of 2 or more units of blood and bleeding that was fatal. Three of the included studies did not report an explicit definition for MB. Consistency in the reporting of outcome definitions is essential for accurate interpretations of results; this applies to other outcomes also. Whilst, the inconsistent reporting of MB definition did not majorly impact the network meta-analysis results and interpretation, researchers should aim to use standardised major bleeding definitions. To give an example, the Subcommittee on Control of Anticoagulation of the International Society on Thrombosis and Haemostasis (ISTH) published an agreed MB definition in 2010.(57)

Some limitations need to be acknowledged, though. Our search cut-off date is 19 June 2017 which means that some relevant trials might have been published after this date. Further searches were conducted up to 22 May 2019. From these, two additional RCTs were identified. (58, 59) Each investigated a new intervention to add to the network, so their results would not affect the relative efficacy estimates reported in our results. A summary of these two trials has been included in the appendix (page 53).

The uncertainty in the results of the PE and MB networks, which is in line with all previously published analyses in this area, is primarily due to the sparse data and the low event rates reported in the RCTs. This means that no clear interpretation can be drawn from the two networks other than what is biologically plausible. However, in absence of any better estimates, the point estimates obtained from these analyses should be taken into account.

Network meta-analysis is a particularly powerful and useful meta-analysis technique, however, to be properly undertaken we have to ensure that included trials are sufficiently homogeneous with similar inclusion and exclusion criteria as well as outcome definitions. This ensures minimisation of confounders. The inconsistency in outcomes' definitions in the included studies, particularly for the MB outcome, is an inherent limitation in the body of evidence in this area that has to be acknowledged. Future trials should use standardised definitions as discussed above.

Finally, formal NICE processes followed in these analyses have not been established for assessing the overall risk of bias associated with network meta-analyses. Risk of bias assessment conducted as part of the systematic review provided a risk of bias rating for the body of evidence that was included in the network meta-analyses. Whilst the risk of bias assessment did not explicitly inform the findings in this manuscript, it informed the decision-making process during the development of the NG89 guideline.

The network meta-analyses results provided a coherent set of relative efficacy estimates which informed the guideline committee's decision-making and was used to populate the economic model that assessed the cost-effectiveness of these strategies for VTE prevention in the eTKR surgery population.(60) A practice recommendation was made by the guideline committee offering clinicians a choice of a number of safe and effective prophylaxis strategies, while emphasising the need for taking into account clinical and patient-related factors when prescribing a VTE prophylaxis strategy.

In conclusion, this systematic review and network meta-analyses summarise the current evidence-base for mechanical and pharmacological VTE prophylaxis strategies in the eTKR surgery population. The results showed that single prophylaxis strategies are more effective in prevention of DVT in this population compared to combined prophylaxis, with rivaroxaban being most effective. The results provide a consistent set of relative treatment effects, and their associated uncertainty, that could be used in economic models to assess the cost effectiveness of these strategies in any jurisdiction. Further research is needed, however, to address the issues identified in the PE and MB networks, particularly the low event rates and its impact on uncertainty of the results.

Authors' contributions

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

Declaration of interests

This work was undertaken by the National Guideline Centre (NGC), Royal College of Physicians London which received funding from the National Institute for Health and Care Excellence (NICE). Ms Lewis, Ms Glen, Dr Dawoud, Ms Cobb and Mr Sharpin report grants from NICE during the conduct of the study. Dr Dias reports grants from Centre for Guidelines (NICE) , grants from UK Medical Research Council, during the conduct of the study; grants from Pfizer, outside the submitted work. Mr Griffin reports grants from NIHR Clinician Scientist (Open Fracture Management, grants from NIHR RfPB Programme (TULIP trial) , grants from NIHR SRP (Hip fracture review portfolio) , grants from NIHR RfPB Programme (WHiTE5 definitive trial) , grants from NIHR HTA Programme (TRAFFix Trial) , grants from NIHR RfPB Programme (WHiTE5 feasibility) , grants from X-Bolt Commercial Grant (Investigator Initiated), outside the submitted work. Professor Reed reports personal fees from Zimmer, grants from Heraeus cement, grants from ConvaTec, grants and personal fees from ASHN/Heraeus, grants from The Health Foundation, grants and personal fees from Stryker, grants from Heraeus, grants from Orthopaedic Research UK, grants from Orthopaedic Research UK, grants from AR-UK, grants and personal fees from 3m Healthcare, grants and personal fees from The Health Foundation, grants from OR-UK, grants from Curetis, grants and personal fees from Heraeus, grants and personal fees from NHSI, Vifor Pharma, Shuelke, Northumbria NHS Vangaurd, grants from Depuy, Stryker, Zimmer Biomet, Biocomposites, Aquilant, Heraeus, personal fees from Zimmer Bioment, personal fees from Heraeus, personal fees from Stryker, other from ConvaTec, outside the submitted work. Mr. Rossiter has nothing to disclose. Professor Stansby has nothing to disclose. Dr. Barry reports personal fees from Royal College of Physicians, during the conduct of the study.

Ethics approval statement

No ethics approval was required for this review.

Acknowledgements

National Institute for Health and Care Excellence for funding “Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. Available from https://www.nice.org.uk/guidance/ng89. (2018)”. NICE Decision Support Unit (DSU) Team for their input. NICE guideline committee members and in particular the patient representatives, for their contribution to the discussions around the design of the study and interpretation of the results.

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Supporting Information

See separate appendix *document*