

Graduated compression stockings for the prevention of deep-vein thrombosis in postoperative surgical patients: a systematic review and economic model with a value of information analysis

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Declared competing interests of authors: none

Published November 2015

DOI: 10.3310/hta19980

Scientific summary

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Health Technology Assessment 2015; Vol. 19: No. 98

DOI: 10.3310/hta19980

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Scientific summary

Background

Deep-vein thrombosis (DVT) can occur in hospitalised patients owing to changes in the blood vessel wall, changes in blood flow and changes in the properties of the blood, caused by factors such as immobilisation and excessive body fluid loss.

Routine prophylaxis reduces morbidity, mortality and health-service costs in hospitalised patients at risk of DVT. Prophylaxis can be pharmacological [such as low-molecular-weight heparin (LMWH)] and/or mechanical [such as graduated compression stockings (GCSs)].

Graduated compression stockings are available as knee-length or thigh-length stockings. The National Institute for Health and Care Excellence (NICE) guideline on venous thromboembolism [NICE. *NICE Clinical Guideline CG92: Venous Thromboembolism: Reducing the Risk: Reducing The Risk of Venous Thromboembolism (Deep Vein Thrombosis and Pulmonary Embolism) in Patients Admitted to Hospital*. London: NICE; 2010] states that the length of stockings is a controversial issue and there is no clear randomised evidence that one length is more effective than another.

Objectives

The aim of this research was to establish the expected value of undertaking additional research comparing the relative effectiveness of thigh-length versus knee-length GCSs, in addition to standard pharmacoprophylaxis, for prevention of DVT in surgical patients. There are two key objectives:

- to undertake a systematic review to estimate clinical effectiveness and inform key clinical parameters for a decision model
- to develop a decision model to estimate cost-effectiveness and to undertake a value of information (VOI) analysis.

Methods of clinical evidence reviews

Four key clinical areas were assessed to inform the decision model:

- i. the relative effectiveness of thigh-length versus knee-length stockings for prevention of DVT in surgical patients
- ii. baseline risk of DVT
- iii. the clinical consequences of DVT
- iv. patient adherence.

A systematic approach to identifying the evidence was undertaken to inform these parameters.

Effectiveness of thigh-length versus knee-length stockings

Eleven databases were searched up to August 2013 for reviews of GCSs. The included and excluded studies listed by relevant systematic reviews were screened for relevant primary studies. To update the searches undertaken in the relevant reviews, systematic searches for randomised controlled trials (RCTs) published since January 2010 were undertaken in February 2014. Six electronic sources were searched as well as two grey literature databases. No language restrictions were applied.

Randomised controlled trials assessing thigh-length or knee-length GCSs in surgical patients were eligible for inclusion; however, the length of stocking had to be clearly stated. The primary outcome was incidence of DVT. Complications associated with DVT and adverse events related to the use of GCSs were also assessed.

An analysis of the data was performed using odds ratios (ORs) along with 95% confidence intervals (CIs). Owing to the clinical and methodological variation between trials, a random-effects model was used to pool data. The I^2 -statistic was used to quantify statistical heterogeneity.

Data on the incidence of pulmonary embolism (PE), mortality and adverse events related to the use of GCSs were tabulated and synthesised narratively.

A network meta-analysis (NMA) was undertaken for the outcome DVT, as this was the only outcome for which there was sufficient evidence to perform an NMA. LMWH, low-dose heparin and fondaparinux were assumed to have the same effectiveness. Based on the advice of the clinical advisors, it was assumed that there was no stocking–heparin interaction in the base-case analysis. This assumption was tested in a sensitivity analysis. A random-effects analysis was used and credible intervals (CrIs) represent the uncertainty around the average treatment effect across trials.

The only potential effect modifier for which there was evidence across the trials and a relevant network was whether or not patients had undergone orthopaedic surgery, and subgroup analyses were conducted for this.

Baseline risk of deep-vein thrombosis

Existing guidelines on the risk of DVT in surgical populations were identified and the source of synthesised evidence considered most appropriate was based on the scope and quality of the evidence and was used to inform the economic model.

The clinical consequences of deep-vein thrombosis (mortality and morbidity)

To identify the best available evidence regarding the clinical consequences of DVT, the library of records identified for the review of effectiveness was screened. The source of synthesised evidence on the clinical consequences of DVT considered most appropriate to inform the economic model was identified based on the scope and quality of the review/guidelines.

Patient adherence and preference

The library of records identified for the review of effectiveness was checked for studies (trials and observational studies) assessing patient adherence and preference. Given the heterogeneity between the studies and the limited outcome data reported, the data are presented in tables and as a narrative synthesis.

Results of clinical evidence reviews

Effectiveness of thigh-length versus knee-length stockings

Twenty-three RCTs were included in the systematic review. There was substantial variation between the included trials in terms of the patient characteristics, interventions and methods of outcome assessment.

Deep-vein thrombosis results

Twenty RCTs reported rates of DVT and provided sufficient data to be included in meta-analyses. Where reported, the majority of DVTs were asymptomatic, the clinical consequences of which are unknown.

Two trials directly compared knee-length with thigh-length GCSs plus pharmacological prophylaxis; results were inconsistent in terms of the direction of effect. Reasons for the inconsistent findings between the two trials were unclear and may be because of chance.

Five trials comparing knee-length with thigh-length GCSs with or without pharmacological prophylaxis were pooled; the summary estimate of effect indicated a trend favouring thigh-length GCSs, but the findings were not statistically significant (OR 1.48, 95% CI 0.80 to 2.73).

Network meta-analysis

Thirteen trials contained data that directly or indirectly informed the relative effectiveness of thigh-length versus knee-length stockings with or without pharmacological prophylaxis for the prevention of DVT and were included in the NMA. There was significant statistical heterogeneity in the models and inconsistency indicating that there may be underlying unknown clinical and methodological heterogeneity across the trials. In the base-case analysis, thigh-length stockings with pharmacological prophylaxis were more effective than knee-length stockings with pharmacological prophylaxis (knee vs. thigh OR 1.76, 95% CrI 0.82 to 3.53), but this result was not statistically significant. Overall, thigh-length stockings with pharmacological prophylaxis was the most effective treatment, with a 0.73 probability that it would be the most effective treatment in a new trial of all treatments.

Pulmonary embolism, mortality and adverse event results

Pulmonary embolism events and VTE-related mortality events were generally rare in the included trials that reported these outcomes. Adverse events were rarely reported, and those related to GCSs were minor events, including minor foot abrasions, superficial thrombophlebitis or the stocking slipping down.

Baseline risk of deep-vein thrombosis

Thirteen potentially relevant guidelines were identified from the literature search. The most comprehensive and rigorous guidelines for orthopaedic and non-orthopaedic patients were published by NICE [NICE 2010; and NICE. *Venous Thromboembolism: Reducing the Risk. Evidence Update February 2012: A Summary of Selected New Evidence Relevant to NICE Clinical Guideline 92 'Reducing the Risk of Venous Thromboembolism (Deep Vein Thrombosis and Pulmonary Embolism) in Patients Admitted to Hospital' (2010)*. London: NICE; 2012] and the American College of Chest Physicians (ACCP) (Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA. Prevention of VTE in nonorthopedic surgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;**141**:e195S–e226S; and Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos A-M, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th edn: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;**141**:e691S–e736S). However, the studies used to calculate baseline risks in the NICE guidelines were considered out of date and not appropriate to inform the economic model. Owing to limited reporting in the ACCP guidelines, the authors of the ACCP guidelines were contacted for further information and a meta-analysis was undertaken to pool the studies included in the ACCP guidelines. We estimated the baseline risk of symptomatic DVT to range from 0.38% for total hip replacement (THR) to 1.23% for high-risk general surgery (GS) and from 1.81% to 19.76% for total DVT.

The clinical consequences of deep-vein thrombosis (mortality and morbidity)

The NICE guidelines were considered the most directly relevant sources of synthesised evidence for the economic model; the estimates of the consequences of DVT were based on a search for good-quality systematic reviews and economic evaluations into baseline risks for post-thrombotic syndrome (PTS), pulmonary hypertension (PHT) and stroke. However, the NICE guidelines did not provide estimates for recurrence of VTE. A study by Baglin *et al.* (Baglin T, Douketis J, Tosetto A, Marcucci M, Cushman M, Kyrle P, *et al.* Does the clinical presentation and extent of venous thrombosis predict likelihood and type of recurrence? A patient-level meta-analysis. *J Thromb Haemost* 2010;**8**:2436–42) was identified as a source for recurrent VTE event rates and this, along with the NICE guideline estimates, were used to inform the economic model.

Patient adherence and preference

Nine RCTs and seven observational studies reported data on patient adherence and/or preference.

Patient adherence (wearing stockings correctly) was generally higher with knee-length stockings than thigh-length stockings. However, the studies reflect patient adherence in a hospital setting only, where patients are observed by health-care professionals; it is likely that adherence is lower after patients have been discharged from hospital. Patients preferred knee-length stockings over thigh-length stockings.

Systematic review of cost-effectiveness evidence

Methods of the systematic review of the cost-effectiveness evidence

Systematic searches of the literature were conducted to identify potentially relevant studies for inclusion in the assessment of the cost-effectiveness of GCSs for the prevention of DVT in postoperative surgical patients. Searches undertaken by NICE up to 2008 were updated to 2014.

Results of the systematic review of the cost-effectiveness evidence

No existing economic evaluations were found comparing the different types of GCSs. The prevention of DVT in postoperative surgical patients, however, has been the subject of a full economic evaluation in two previous NICE clinical guidelines (CGs) and three previous NICE single technology appraisals (STAs). The economic models were not available in two of the NICE STAs. Three economic models were available and have been reviewed.

The decision model and cost-effectiveness results

Development of the decision model

Decision problem

A decision-analytic model was developed to assess formally the cost-effectiveness of using knee-length versus thigh-length GCSs in hospital for the prevention of DVT in postoperative surgical patients from the perspective of the UK NHS and Personal Social Services. The interventions being compared were LMWH alone, thigh-length GCSs plus LMWH and knee-length GCSs plus LMWH. The decision model evaluates five surgical population subgroups: THR, total knee replacement (TKR), low-risk GS patients, moderate-risk GS patients and high-risk GS patients. Outcomes are expressed in terms of quality-adjusted life-years (QALYs) and costs are expressed in GBPs. Both costs and QALYs are evaluated over a lifetime horizon and discounted using a 3.5% annual discount rate.

Model description

A two-stage modelling approach was adopted to model the VTE pathway, informed by the findings of the cost-effectiveness review. The initial VTE episodes are modelled for the acute period (14 days post surgery) using a decision tree, and long-term consequences of VTE episodes were modelled using a Markov model. The relative effect estimates used in the model came from the systematic search and NMA. The relative effects were applied to the acute period of the model. The baseline risks of PE, asymptomatic and symptomatic DVT, and bleeding used in the model came from the systematic search and meta-analysis. Long-term consequences included in the model were PTS, PHT, stroke and VTE recurrence. Intervention and event costs were obtained from public sources.

Cost-effectiveness results of the decision model

Compared with LMWH alone, our findings suggest that the adjunctive use of GCSs appears to represent good value for money to the NHS across the different populations considered. In the TKR, GS moderate- and high-risk populations, LMWH alone was dominated by GCSs plus LMWH. In the GS low-risk population, thigh-length GCSs plus LMWH had an incremental cost-effectiveness ratio (ICER) of £2632 per QALY compared with LMWH alone. However, in the population with the lowest risk of DVT (THR) the cost-effectiveness of adding compression stockings to LMWH alone appeared more finely balanced, with an ICER of £30,366 per QALY. However, even within this population, compression stockings could be cost-effective assuming that the local prices taken into account in the scenario analyses are more representative of prices actually paid in the NHS, with an ICER of £18,900 per QALY. These general findings are consistent with the findings of the previous NICE CG which reported favourable cost-effectiveness estimates for GCSs combined with pharmacological prophylaxis.

In contrast to the previous NICE guideline, our analysis was also able to explore differences in cost-effectiveness between the different types of stockings. Importantly, our results consistently found that the use of thigh-length GCSs plus LMWH appeared to dominate knee-length GCSs plus LMWH. These findings appeared robust to alternative assumptions relating to the acquisition costs and adherence.

Value of information analysis and future research priorities

The results of the expected value of perfect information (EVPI) analysis ranged from £4.7M to £119.7M in the base-case analysis using the random-effects NMA and considering all three strategies at a threshold of £20,000 (£7.5M to £145.9M at £30,000 threshold). The lowest reported EVPI was £0.20M for the GS low-risk subgroup in the base-case analysis using the fixed-effects NMA and considering only thigh-length GCSs plus LMWH versus knee-length GCSs plus LMWH at a threshold of £20,000. The highest reported EVPI was £179.0M for the GS high-risk subgroup in the 75% adherent scenario using the random-effects NMA and considering all strategies at £30,000 threshold.

Across all analyses, the EVPI remained highest in the high baseline-risk subgroups. This suggests that further research is most valuable in these populations. The expected value of partial perfect information (EVPPi) undertaken supported this finding and demonstrated that the most valuable parameter on which to undertake further research is the relative treatment effect; EVPPi ranged from £2.0M to £39.4M. However, the conclusions depended on the acquisition price of GCSs, the expected adherence to thigh-length GCSs and whether or not uncertainty could be resolved around possible effect modifiers.

Discussion

The analyses undertaken support previous analyses that have demonstrated the uncertainty in the relative effect of thigh-length GCSs versus knee-length GCSs. The analyses further suggest that GCSs are cost-effective as add-ons to prophylaxis drug treatment, and that thigh-length GCSs dominates knee-length GCSs. The VOI is highest for the relative effect parameters in the highest risk patients (those with a symptomatic DVT risk of 1.23% or an overall DVT risk of 19.76%). Changes in patient characteristics and treatment patterns are likely to affect the baseline risk of DVT, for example, the use of new oral anticoagulant treatments that lower the risk of DVT will lower the value of evidence collection on the relative effect of knee- versus thigh-length stockings.

Conclusions

The analysis revealed that further research should focus on resolving uncertainty in the relative effectiveness of thigh-length GCSs versus knee-length GCSs, in particular in high-risk subgroups of patients in whom the value of further research is most evident. However, the efficiency of this research (i.e. whether or not this represents value for money) is dependent on several factors, including the acquisition price of GCSs, the expected adherence to thigh-length GCSs and whether or not uncertainty can be resolved around possible effect modifiers as well as the feasibility and actual cost of undertaking the proposed research.

Study registration

This study is registered as PROSPERO CRD42014007202.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 5.116

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index.

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 13/72/01. The contractual start date was in January 2014. The draft report began editorial review in August 2014 and was accepted for publication in May 2015. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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