Compression stockings in addition to low-molecular-weight heparin to prevent venous thromboembolism in surgical inpatients requiring pharmacoprophylaxis: the GAPS non-inferiority RCT

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Scientific summary

The GAPS RCT

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Scientific summary

Background

Venous thromboembolism encompassing deep-vein thrombosis and pulmonary embolism is a leading cause of preventable death in patients admitted to hospital. In addition, just under half of patients with deep-vein thrombosis will go on to develop a post-thrombotic limb, representing significant health burden and societal costs. Surgical patients are at an increased risk of venous thromboembolism, but effective venous thromboembolism prophylaxis can reduce the risk in this group by half.

In 2005, the Department of Health and Social Care commissioned the National Institute for Health and Care Excellence to produce guidance on measures to prevent venous thromboembolism for surgical patients. The guideline recommended that surgical patients assessed as being at a moderate or high risk of venous thromboembolism, in whom there are no contraindications and who are at a low risk of major bleeding, should receive both pharmacological thromboprophylaxis, such as low-molecular-weight heparin, and mechanical thromboprophylaxis in the form of graduated compression stockings.

The benefit of graduated compression stockings has recently been called into question, and a systematic review found limited evidence to support the use of graduated compression stockings in addition to pharmaco-thromboprophylaxis in surgical inpatients. Patients' 'real world' experience of stockings is poor and is associated with a number of undesired effects, including discomfort, ischaemia and blistering. The risk of venous thromboembolism needs to be balanced against the risk of preventative measures, both mechanical and pharmacological.

Objectives (list of research questions)

1. Primary objective: to determine whether or not low-dose low-molecular-weight heparin alone is non-inferior to a combination of low-dose low-molecular-weight heparin plus graduated compression stockings for the prevention of venous thromboembolism in adult elective surgical inpatients.
2. Secondary objectives:

    i. to profile the adverse effects of graduated compression stockings and low-molecular-weight heparin
    ii. to determine compliance with low-molecular-weight heparin and/or graduated compression stockings during admission
    iii. to compare quality of life between those receiving low-molecular-weight heparin alone and those receiving both low-molecular-weight heparin and graduated compression stockings
    iv. to provide evidence to support future guidance and policy in venous thromboembolism prevention.

Methods

Design

A multicentre, prospective, non-inferiority randomised controlled trial to compare venous thromboembolism outcomes in surgical inpatients assessed as being at a moderate or high risk of venous thromboembolism who are prescribed graduated compression stockings in addition to low-dose low-molecular-weight heparin with those prescribed low-dose low-molecular-weight heparin alone.

Setting
Seven secondary care NHS hospitals across England performing a variety of surgical procedures.

Participants
Between May 2016 and 31 January 2019, 1905 participants were randomised into the graduated compression as an adjunct to thromboprophylaxis in surgery (GAPS) trial. Follow-up was completed on 1 May 2019. Written informed consent was obtained from all participants, who then underwent eligibility assessments. Participants who met the inclusion and exclusion criteria were randomised 1 : 1 to either low-molecular-weight heparin alone (intervention) or low-molecular-weight heparin plus graduated compression stockings (standard care).

Inclusion criteria

- Elective surgical inpatients assessed as being at a moderate or high risk of venous thromboembolism according to the widely-used UK NHS England venous thromboembolism risk assessment tool for venous thromboembolism (or the trust equivalent based on this form) (based on the National Institute for Health and Care Excellence recommendations).
- Able to give informed consent to participate in the trial after reading the patient information documentation.
- Aged $\geq$ 18 years.

Exclusion criteria

- Contraindications to low-molecular-weight heparin.
- Contraindications to graduated compression stockings, including peripheral arterial disease, stroke patients and individuals undergoing lower limb surgery.
- Documented or known thrombophilia or thrombogenic disorder.
- Individuals requiring therapeutic anticoagulation.
- Previous venous thromboembolism.
- Patients having intermittent pneumatic compression beyond theatre and recovery.
- Patients requiring inferior vena cava filter.
- Pregnancy (female participants of reproductive age were eligible for inclusion in the trial, subject to a negative pregnancy test prior to randomisation and again on the day of surgery if there was a possibility of pregnancy since the last test).
- Patients requiring thromboprophylaxis to be extended beyond discharge.
- Application of a cast or brace in theatre.

Randomisation
Randomisation (1 : 1) was web based and hosted by the Centre for Healthcare Randomised Trials. A minimisation algorithm incorporating centre, moderate or high risk of venous thromboembolism and sex was used in addition to an incorporated random element.

Interventions
Graduated compression stockings, sometimes known as medical compression stockings or anti-embolism stockings, work by exerting pressure at the ankle that gradually decreases up the garment to the knee or thigh. The pressure gradient ensures that blood flows towards the heart, minimising reflux to the foot or laterally into the superficial veins.

Low-molecular-weight heparins at a thromboprophylactic dose are a safe and effective agent for the prevention of venous thromboembolism, particularly as they do not require regular monitoring or require dose adjustments. This has led to their increased use as thromboprophylaxis in both medical and surgical patients.

Outcomes and follow-up

The primary outcome was symptomatic or asymptomatic venous thromboembolism up to 90 days after surgery, which was confirmed by imaging (duplex ultrasound scan performed between days 14 and 21 after surgery or, if clinical suspicion, at any time up to 90 days after surgery). Secondary outcomes included quality of life over 90 days, as measured by a generic health-related quality-of-life tool, EuroQol-5 Dimensions, five-level version; compliance with low-molecular-weight heparin and graduated compression stockings, as measured against hospital drug charts and self-report participant diaries; and overall mortality.

Participants in both treatment arms were followed up at 7 days post surgery or at discharge (whichever was earlier). Low-molecular-weight heparin compliance, graduated compression stockings compliance (in the graduated compression stockings arm alone) and imaging-confirmed venous thromboembolism were recorded by the research nurse. All patients were invited to return to hospital between 14 and 21 days after surgery to undergo a full bilateral duplex ultrasound scan of their legs carried out by a vascular scientist. The final follow-up was conducted 90 days after surgery to record health resource use and imaging-confirmed venous thromboembolism. The EuroQol-5 Dimensions, five-level version, was administered at baseline and at each follow-up either in person or via the telephone, or the patient could self-complete electronically via the database.

Results (research findings)

A total of 1905 participants were randomised, of whom 1858 were included in the intention-to-treat analysis. A primary outcome event occurred in 16 out of 937 (1.7%) patients in the low-molecular-weight heparin-alone arm compared with 13 out of 921 (1.4%) in the low-molecular-weight heparin plus graduated compression stockings arm. The risk difference between low-molecular-weight heparin alone and low-molecular-weight heparin plus graduated compression stockings was 0.30% (95% confidence interval −0.65% to 1.26%). As the 95% confidence interval did not cross the non-inferiority margin of 3.5% ($p < 0.001$), the non-inferiority of low-molecular-weight heparin alone was shown.

Conclusions

The results of the GAPS trial indicate that among elective surgical patients assessed as being at a moderate or high risk of venous thromboembolism, administration of pharmacological thromboprophylaxis alone is non-inferior to a combination of pharmacological thromboprophylaxis plus graduated compression stockings.

Implications for health care

Findings from this trial suggest that in elective surgical patients requiring pharmacological thromboprophylaxis, adjuvant graduated compression stockings are unlikely to be of benefit.

Recommendations for research (numbered in priority order)

1. Examination of stakeholders' views of the findings of the GAPS trial and its impact on future clinical practice.
2. Randomised trial of inpatient graduated compression stockings use versus no inpatient graduated compression stockings use in patients requiring extended pharmacological thromboprophylaxis (while inpatient and beyond hospital discharge) following surgery.
3. Randomised trial to evaluate whether or not adjuvant graduated compression stockings have a role in patients undergoing emergency surgical procedures.
4. Randomised trial of patients assessed as being at a low risk of venous thromboembolism: inpatient graduated compression stockings use versus no inpatient graduated compression stocking use.

Trial registration

This trial is registered as ISRCTN13911492.

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This report

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