Thigh-Length Versus Below-Knee Stockings for Deep Venous Thrombosis Prophylaxis After Stroke
A Randomized Trial

The CLOTS (Clots in Legs Or sTockings after Stroke) Trial Collaboration*

Background: Graduated compression stockings are widely used for deep venous thrombosis (DVT) prophylaxis. Although below-knee stockings are used more often than thigh-length stockings, no reliable evidence indicates that they are as effective as thigh-length stockings.

Objective: To compare the effectiveness of thigh-length stockings with that of below-knee stockings for preventing proximal DVT in immobile, hospitalized patients with stroke.

Design: Parallel-group trial with centralized randomization (minimization within centers) to ensure allocation concealment. The ultrasonographers who looked for DVT were blinded, but the patients and caregivers were not. (Controlled-trials.com registration number: ISRCTN28163533)

Setting: 112 hospitals in 9 countries.


Intervention: 1552 patients received thigh-length stockings and 1562 patients received below-knee stockings to wear while they were in the hospital.

Measurements: Ultrasonographers performed compression duplex ultrasonography in 1406 patients (96% of survivors) in each treatment group between 7 and 10 days after enrollment. They performed a second scan in 643 patients in the thigh-length stockings group and 639 in the below-knee stockings group at about 25 to 30 days. The primary outcome was symptomatic or asymptomatic DVT in the popliteal or femoral veins, detected on either scan.

Results: Patients were retained in their assigned group for all analyses. The primary outcome occurred in 98 patients (6.3%) who received thigh-length stockings and 138 (8.8%) who received below-knee stockings (absolute difference, 2.5 percentage points [95% CI, 0.7 to 4.4 percentage points]; P = 0.008), an odds reduction of 31% (CI, 9% to 47%). Seventy-five percent of patients in both groups wore the stockings for 30 days or until they were discharged, died, or regained mobility. Skin breaks occurred in 61 patients who received thigh-length stockings (3.9%) and 45 (2.9%) who received below-knee stockings.

Limitation: Blinding was incomplete, 2 scans were not obtained for all enrolled patients, and the trial was stopped before the target accrual was reached.

Conclusion: Proximal DVT occurs more often in patients with stroke who wear below-knee stockings than in those who wear thigh-length stockings.

Primary Funding Source: Medical Research Council of the United Kingdom, Chief Scientist Office of the Scottish Government, and Chest Heart and Stroke Scotland.


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Conversion of graphics into slides
Context
Are either thigh-length or below-knee stockings better for reducing risk for deep venous thrombosis (DVT) in patients with stroke?

Contribution
This large randomized trial involved immobile patients with acute stroke. Patients had ultrasonography 7 to 10 days after hospitalization and then again 15 to 20 days after that. Proximal DVT was detected in 6.3% and 8.8% of those who received thigh-length or below-knee stockings, respectively. Skin breaks occurred in 3.9% of those who received thigh-length stockings and 2.9% of those who received below-knee stockings.

Caution
Not all patients had both ultrasonography scans.

Implication
Proximal DVT occurs more commonly with below-knee stockings than with thigh-length stockings in immobile patients with stroke.

—The Editors

About 200 to prevent 1 proximal DVT. In CLOTS Trial 2, reported here, we aimed to compare the effectiveness of thigh-length and below-knee stockings for preventing proximal DVT in immobile, hospitalized patients with stroke.

Methods
Design Overview
CLOTS Trial 2 was a multicenter, international, parallel-group design with a centralized randomization system that allocates treatment in a 1:1 ratio that ensured allocation concealment. We aimed to blind the ultrasonographers who scanned for DVT to allocation group, but the patients and their caregivers could not be blinded because of the nature of the intervention. We enrolled the first patient on 14 January 2002 and the last on 28 May 2009 and completed follow-up in February 2010. The Multicentre Research Ethics Committees in the United Kingdom and the local ethics committees of all contributing centers approved our protocol. Written informed consent was obtained from all patients or from a valid proxy for patients who lacked the mental capacity.

During the trial, we adapted our protocol so that centers in countries with short lengths of hospital stay and less robust systems for central follow-up at 6 months could participate. The adapted protocol, which we called “CLOTS Lite,” was identical to our original protocol except that centers were requested to perform compression duplex ultrasonography once for each patient at 7 to 10 days after random assignment, regardless of whether the patient remained in the hospital, and follow-up data were not collected at 6 months.

In 2009, the results of CLOTS Trial 1 were published (8) and showed that thigh-length stockings were not associated with a clinically worthwhile reduction in proximal DVT but caused skin breaks. The Steering Committee, advised by the Data Monitoring and Ethics Committee, decided to stop enrollment in CLOTS Trial 2 early because it was unreasonable to expose patients with acute stroke to the discomfort and risk of thigh-length stockings. Although we had exceeded our recruitment target of 2500 patients by then, the DVT rate was lower than expected—only 236 patients (79% of our target) had had proximal DVT, our primary outcome.

Setting and Participants
Our collaborators in 112 centers (Appendix, available at www.annals.org) enrolled 3114 patients. Of these, 3014 patients were recruited by hospitals in the United Kingdom, Italy, the Republic of Ireland, Australia, and the Czech Republic, which participated under the original protocol. Single centers in Portugal, India, Canada, and Mexico recruited 100 additional patients under CLOTS Lite. To participate, hospitals had to have a local principal investigator who would take responsibility for trial governance, a well-organized inpatient stroke service, a nursing staff trained in the use of stockings, and a diagnostic ultrasonography department that routinely performed compression duplex ultrasonography.

Patients were eligible for inclusion if they were hospitalized within 1 week of an acute stroke (ischemic or hemorrhagic), could be enrolled between the day of admission (day 0) and day 3 in the hospital, and were immobile (could not walk independently to the toilet). We excluded patients with subarachnoid hemorrhage and those with severe peripheral vascular disease or diabetic or sensory neuropathy. We did not require the centers to keep screening logs of eligible patients.

Random Assignment and Interventions
Having obtained consent, the clinician entered the patient’s baseline data into our computerized central randomization service by means of a secure Web interface or a touch-tone telephone system. After the computer program checked these baseline data for completeness and consistency, it allocated that patient to receive either routine care plus thigh-length stockings or routine care plus below-knee stockings. The system applied a minimization program to achieve balance within the centers for 4 prognostic factors: delay since stroke onset (day 0 or 1 vs. day ≥2); stroke severity with a validated prognostic model (9); leg weakness (able to lift both legs or not); and prescription of heparin, warfarin, or alteplase. Minimization randomly allocates the first patient to a treatment, but allocates each subsequent patient to the treatment that leads to the least difference between the treatment groups with respect to the prognostic factors (10). Because simple minimization
We coded the reason why a scan was not performed; however, if a patient was not scheduled for a scan but died, then that death would not be recorded here. Therefore, the numbers of deaths are not the same as those in Tables 2 and 3. CLOTS = Clots in Legs Or sTockings after Stroke.
Within centers can in theory lead to alternation of treatment allocation, our system also incorporated a degree of random allocation; it allocated patients to the treatment group that minimized the difference between the groups with a probability of 0.8 rather than 1.0. This helped to guarantee allocation concealment.

Nursing staff applied the allocated length and size of the T.E.D. stockings, on the basis of the manufacturer’s fitting instructions, to both legs. The stockings were then to be worn day and night until the patient was independently mobile, discharged from the hospital, or declined to wear the stockings or until the staff became concerned about the patient’s skin. Our protocol stated that stockings should be worn until discharge but did not explicitly state that they should be removed at hospital discharge; this was left to the discretion of local clinicians. Our recruitment coordinator and representatives of Tyco Healthcare provided on-site training to nursing staff in the correct sizing, fitting, and monitoring of stockings, which was supplemented by a training video and Web-based training. Nursing staff was asked to record their use of stockings on the medication chart to increase adherence and aid monitoring. We stipulated that both treatment groups should receive the same routine care, which could include early mobilization, hydration, or antiplatelet or anticoagulant drugs, depending on local protocols. The local coordinator extracted information from the medication charts on adherence to stocking instructions and use of antiplatelet or anticoagulant drugs during the hospital stay and recorded this on the hospital discharge form, so we could check that these aspects of routine care were used equally in the treatment groups.

### Outcomes and Follow-up

The primary outcome was the occurrence of symptomatic or asymptomatic DVT in the popliteal or femoral veins (detected on the first or second compression duplex ultrasonography performed as part of the trial protocol) or symptomatic DVT in the popliteal or femoral veins, confirmed on imaging (compression duplex ultrasonography or venography) within 30 days of random assignment. We focused on proximal DVT because it is much more reliably detected by ultrasonography and is considered to be clinically more important (11, 12).

The secondary outcomes reported here were deaths from any cause; any DVT, symptomatic or asymptomatic, that affected the calf, popliteal, or femoral veins; symptomatic DVT that affected the calf, popliteal, or femoral veins; or venous thromboembolic events or deaths from any cause within 6 months of random assignment.

### Table 1. Baseline Characteristics of Patients Enrolled in CLOTS Trial 2

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Thigh-Length Stockings Group (n = 1552)</th>
<th>Below-Knee Stockings Group (n = 1562)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), y*</td>
<td>76 (67–83)</td>
<td>75 (67–82)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>813 (52.4)</td>
<td>727 (46.5)</td>
</tr>
<tr>
<td>Final diagnosis at hospital discharge, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1262 (81.3)</td>
<td>1269 (81.2)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>176 (11.3)</td>
<td>189 (12.1)</td>
</tr>
<tr>
<td>Uncertain type of stroke</td>
<td>55 (3.5)</td>
<td>52 (3.3)</td>
</tr>
<tr>
<td>Not stroke (included in primary analysis)</td>
<td>54 (3.5)</td>
<td>46 (2.9)</td>
</tr>
<tr>
<td>Missing (no discharge form)</td>
<td>5 (0.3)</td>
<td>5 (0.3)</td>
</tr>
<tr>
<td>Stroke unknown</td>
<td>0 (0.0)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>History and risk factors, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous DVT or pulmonary emboli</td>
<td>82 (5.3)</td>
<td>67 (4.3)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>271 (17.5)</td>
<td>263 (16.8)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>32 (2.1)</td>
<td>32 (2.1)</td>
</tr>
<tr>
<td>Overweight (informal assessment)</td>
<td>458 (29.5)</td>
<td>474 (30.3)</td>
</tr>
<tr>
<td>Current cigarette smoker</td>
<td>285 (18.4)</td>
<td>274 (17.5)</td>
</tr>
<tr>
<td>Independent in daily activities before stroke*</td>
<td>1389 (89.5)</td>
<td>1439 (92.1)</td>
</tr>
<tr>
<td>Lived alone before stroke*</td>
<td>484 (31.2)</td>
<td>534 (34.2)</td>
</tr>
<tr>
<td>Indicators of stroke severity, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Able to lift both arms off bed*</td>
<td>647 (41.7)</td>
<td>646 (41.4)</td>
</tr>
<tr>
<td>Able to talk and oriented in time, place, and person*</td>
<td>1088 (70.1)</td>
<td>1067 (68.3)</td>
</tr>
<tr>
<td>Able to lift both legs off bed</td>
<td>622 (40.1)</td>
<td>625 (40.0)</td>
</tr>
<tr>
<td>Able to walk without help*</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Prescribed heparin, warfarin, or alteplase at baseline, n (%)†</td>
<td>196 (12.6)</td>
<td>203 (13.0)</td>
</tr>
<tr>
<td>Delay from stroke onset to random assignment 0–1 d, n (%)†</td>
<td>707 (45.5)</td>
<td>693 (44.4)</td>
</tr>
<tr>
<td>Stroke severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicted probability of being alive and independent in daily activities 0 and 0.15, n (%)‡‡</td>
<td>842 (54.2)</td>
<td>848 (54.3)</td>
</tr>
<tr>
<td>Median predicted probability of being alive and independent in daily activities (interquartile range) †‡</td>
<td>0.12 (0.03–0.40)</td>
<td>0.12 (0.03–0.39)</td>
</tr>
</tbody>
</table>

CLOTS = Clots in Legs Or sTockings after Stroke; DVT = deep venous thrombosis.

* Included in model to predict probability of being alive and independent at 6 mo (9).
† Included in minimization.
‡ Calculated from baseline variables by using a validated prognostic model (9).
pulmonary emboli, confirmed on imaging (computed tomography pulmonary angiography or ventilation–perfusion isotope scanning) or autopsy; and potential complications of stockings, such as skin breaks, blisters, limb ischemia, or leg amputations, that occurred in the hospital or were confirmed later by scheduled compression duplex ultrasonography. Our findings on survival, functional status, and quality of life at 6 months and occurrence of DVT or pulmonary emboli after 30 days will be published elsewhere.

We aimed to obtain compression duplex ultrasonograms of the veins in both legs for all patients between days 7 and 10 after random assignment and perform a second scan whenever practical between days 25 and 30, even if this required the patient to return to the hospital as an outpatient. Before random assignment, the clinician could elect not to do the second scan if it would be impractical (for example, if the patient would probably be discharged home to another region). We specified this to reduce the number of scheduled second scans not completed and to reduce the risk for bias from differing follow-up rates between the treatment groups. CLOTS Lite centers performed a single scan at 7 to 10 days. The nurses on the ward were instructed to remove the stockings before the scan to avoid unblinding the ultrasonographer. The ultrasonographers recorded whether the patient attended the scan wearing stockings so that we could estimate the degree of unblinding (Figure 1). We defined the minimum acceptable technical standards for ultrasonography equipment and stipulated that the trial ultrasonographers should have performed compression duplex ultrasonography to diagnose DVT as part of a clinical service. We asked them to visualize the popliteal and femoral veins in both legs but did not insist that they routinely visualize the 6 deep veins in the calf, because thrombosis detection in these veins is far less reliable. Our trial radiologist, who was blinded to group allocation, received hard copies of scans with positive results to verify each primary outcome. Scans with negative results were not centrally verified because meaningful verification of static images is difficult with ultrasonography techniques. If the second ultrasonogram was delayed for more than 30 days and showed popliteal or femoral DVT, it was included in the primary outcome. However, we did not include a proximal DVT event in our primary outcome if it came to our attention only because of symptoms that started more than 30 days after enrollment, because this might have introduced bias.

The local coordinator, who could not be blinded to group allocation, reviewed the medical record and extracted the information needed to complete our discharge form. This form included checkboxes for recording the secondary outcomes and adverse events. Coordinators recorded the date of occurrence of any secondary outcome and included a free-text description of the problem. The chief investigator reviewed these data centrally and coded the events while blinded to group allocation, to the extent possible. On rare occasions, inadvertent unblinding occurred because the coordinator mentioned the length of the stockings in their description of an adverse event.

We checked data centrally for completeness and consistency and sent monthly reports to each center with data queries. Our recruitment coordinator visited hospitals regularly to check their trial procedures and to obtain missing data. She did not perform source data verification unless the trial data manager required clarification on specific data items.

In our original protocol, the trial coordinating center in each country obtained follow-up data on secondary out-

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**Table 2. Primary and Secondary Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Thigh-.FormattingEnabled Stockings Group (n = 1552), n (%)</th>
<th>Below-Kanine Stockings Group (n = 1562), n (%)</th>
<th>Difference in Proportion (95% CI), percentage points</th>
<th>Adjusted Odds Ratio (95% CI)*</th>
<th>P Value From Logistic Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>98 (6.3)</td>
<td>138 (8.8)</td>
<td>−2.5 (−0.7 to −4.4)</td>
<td>0.69 (0.53 to 0.91)</td>
<td>0.008</td>
</tr>
<tr>
<td>Alive and free of primary outcome</td>
<td>1246 (80.3)</td>
<td>1213 (77.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died before any primary outcome</td>
<td>170 (10.9)</td>
<td>161 (10.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing†</td>
<td>38 (2.4)</td>
<td>50 (3.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Secondary outcomes, by second compression duplex ultrasonography at ≥30 d</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dead by 30 d</td>
<td>182 (11.7)</td>
<td>174 (11.1)</td>
<td>0.6 (−1.6 to 2.8)</td>
<td>1.05 (0.84 to 1.31)</td>
<td>0.67</td>
</tr>
<tr>
<td>Symptomatic proximal DVT</td>
<td>49 (3.2)</td>
<td>63 (4.0)</td>
<td>−0.9 (−2.2 to 0.4)</td>
<td>0.78 (0.53 to 1.14)</td>
<td>0.19</td>
</tr>
<tr>
<td>Asymptomatic proximal DVT</td>
<td>49 (3.2)</td>
<td>75 (4.8)</td>
<td>−1.6 (−3.0 to −0.3)</td>
<td>0.64 (0.44 to 0.93)</td>
<td>0.02</td>
</tr>
<tr>
<td>Symptomatic DVT (proximal or distal)</td>
<td>85 (5.5)</td>
<td>87 (5.6)</td>
<td>−0.1 (−1.7 to 1.5)</td>
<td>0.98 (0.72 to 1.33)</td>
<td>0.87</td>
</tr>
<tr>
<td>Any DVT (proximal or distal)</td>
<td>177 (11.4)</td>
<td>211 (13.5)</td>
<td>−2.1 (−4.4 to 0.2)</td>
<td>0.82 (0.67 to 1.02)</td>
<td>0.08</td>
</tr>
<tr>
<td>Pulmonary emboli</td>
<td>23 (1.5)</td>
<td>19 (1.2)</td>
<td>0.3 (−0.5 to 1.1)</td>
<td>1.23 (0.66 to 2.26)</td>
<td>0.51</td>
</tr>
<tr>
<td>Any DVT or pulmonary emboli</td>
<td>188 (12.1)</td>
<td>220 (14.1)</td>
<td>−2.0 (−4.3 to 0.4)</td>
<td>0.84 (0.68 to 1.04)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

DVT = deep venous thrombosis.

* Adjusted for delay from onset to random assignment; stroke severity; leg strength at baseline; and use of heparin, warfarin, or alteplase and excluding patients who died before primary outcome or had missing data. Only 1 proximal DVT occurred in the 100 patients enrolled into CLOTS (Clots in Legs Or sTockings after Stroke) Lite; this patient was in the below-knee stockings group.

† Known to be alive with no DVT: no compression duplex ultrasonography was performed.
comes by mailed or telephone questionnaires at about 6 months. CLOTS Lite centers followed patients until only compression duplex ultrasonography had been performed or until hospital discharge, whichever occurred last.

Statistical Analysis

We initially planned to recruit until 300 patients had had our primary outcome. We estimated that we would need 2500 patients to provide 90% power ($\alpha = 0.05$) to identify a 4–percentage point absolute reduction in our primary outcome (from 13% to 9%).

For all analyses, we retained participants in the treatment group to which they were originally assigned. As prespecified, data collected under both the original and the CLOTS Lite protocols were combined, because they shared the same recruitment methodology and primary outcome. We calculated the absolute difference in proportion with an outcome between groups and its 95% CIs. The proportion of patients with primary or secondary outcomes was compared by using odds ratios and 95% CIs, adjusted with logistic regression for the 4 variables included in our minimization algorithm (predicted stroke outcome, delay from stroke onset to random assignment, ability of the patient to lift both legs off the bed, and use of anticoagulants or alteplase). We prespecified subgroup analyses of the effect on the primary outcome, subdivided by 3 baseline variables: time from stroke onset to random assignment (day 0 or 1 vs $\geq 2$); use of heparin, warfarin, or alteplase within the preceding 24 hours versus none; and leg weakness (able to lift leg or not). These subgroups were analyzed with logistic regression, with $P$ values calculated from the change in log likelihood on entering the interaction between the subgroup effect and treatment effect into the model. The trial statistician prepared analyses of the accumulating data, which our independent data monitoring committee reviewed at least once per year. No other person had access to these analyses.

Role of the Funding Source

The trial was funded by the Chief Scientist Office of the Scottish Government, Chest Heart and Stroke Scotland, and the Medical Research Council of the United Kingdom; Tyco Healthcare (Covidien) donated stockings and provided training in their use to participating centers. The funders and Tyco Healthcare had no role in data collection, storage, or analysis; drafting of this report; or the decision to publish this manuscript. We allowed the funding sources to comment on the draft manuscript before final submission. The United Kingdom Stroke Research Network adopted our trial in 2005, and network-funded staff were responsible for enrollment and data collection in many of our United Kingdom centers after that date.

RESULTS

Table 1 shows that the baseline characteristics of the patients in each treatment group were very similar, except that a greater proportion of men and a lower proportion of patients who were independent in activities of daily living before their stroke were allocated to receive thigh-length stockings than below-knee stockings. The median delay from onset to random assignment was 2 days (interquartile range, 1 to 2 days) in both groups.

Figure 1 shows the study flow diagram, which includes the completeness, timing, and success of blinding of
follow-up with the first and second compression duplex ultrasonographies, the reasons we did not scan patients, and the completeness of follow-up to 30 days. It also includes data on the use of anticoagulants after randomization. Ultrasonographers scanned 1406 patients (96% of surviving patients) in each treatment group at about 7 to 10 days. They performed a second scan in 643 patients who received thigh-length stockings and 639 who received below-knee stockings (89% of surviving patients in each group for whom a second scan had been scheduled before random assignment) at about 25 to 30 days.

Table 2 shows the frequency of the primary and secondary outcomes, including death, DVT, and pulmonary emboli, up to 30 days (or later scheduled scan) after enrollment. We detected a proximal DVT (our primary outcome) in 98 of 1552 patients (6.3%) who received thigh-length stockings and in 138 of 1562 (8.8%) who received below-knee stockings, a difference in absolute risk of 2.5 percentage points (CI, 0.7 to 4.4 percentage points; \( P = 0.007 \)) and a difference in odds of 31% (CI, 9% to 47%). This changed little when adjusted for the 4 factors included in our minimization algorithm (\( P = 0.008 \)). We also performed a post hoc analysis that adjusted for sex to account for the baseline imbalance observed (difference in odds, 30% [CI, 8% to 46%]; \( P = 0.011 \)). The differences in DVT rate were largely due to a reduction in proximal rather than distal DVT. Treatment groups did not significantly differ in the number of deaths or pulmonary emboli.

Table 3 shows the results of our prespecified subgroup analyses, which do not suggest any statistically significant interaction between subgroups and the treatment effect for our primary outcome.

Table 3 includes information about adherence with stocking instructions and reasons for removal. Seventy-five percent of patients in both groups wore the stockings for 30 days until they were discharged, died, or regained mobility. Thigh-length stockings were removed more often because of concerns about the skin or patient comfort.

Table 4 shows adverse events reported on the hospital discharge form. Overall, skin problems were more common among patients who received thigh-length stockings (\( P = 0.030 \)), but many were mild. Skin breaks were uncommon, occurring in 61 patients (3.9%) who received thigh-length stockings and 45 patients (2.9%) who received below-knee stockings (odds ratio [OR], 1.38 [CI, 1.03 to 2.04]). Eleven patients had either lower-limb ischemia or amputations, but central review of these cases did not suggest that the stockings had caused or worsened these conditions. The ischemia was most often the result of presumed cardiac embolism from atrial fibrillation.

**DISCUSSION**

Our results show that DVT prophylaxis with below-knee stockings in immobile patients who have had acute stroke is associated with a higher risk for proximal DVT.
Thigh-Length Versus Below-Knee Stockings for DVT Prophylaxis After Stroke

Table 4. Adverse Events

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Thigh-Length Stockings Group (n = 1552)</th>
<th>Below-Knee Stockings Group (n = 1562)</th>
<th>Difference in Proportion (95% CI), percentage points</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value From Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died by day 30, n (%)</td>
<td>182 (11.7)</td>
<td>174 (11.1)</td>
<td>0.6 (−1.6 to 2.8)</td>
<td>1.05 (0.84 to 1.31)</td>
<td>0.67</td>
</tr>
<tr>
<td>Patients with discharge form, n (%)</td>
<td>1550 (99.9)</td>
<td>1560 (99.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median length of hospital stay (IQR), d</td>
<td>19 (10 to 42)</td>
<td>20 (10 to 45)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events, n (%)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-severity skin problems</td>
<td>75 (4.8)</td>
<td>56 (3.6)</td>
<td>1.2 (−0.2 to 2.7)</td>
<td>1.37 (0.96 to 1.94)</td>
<td>0.08</td>
</tr>
<tr>
<td>Patients with skin breaks, ulcers, blisters, or necrosis</td>
<td>61 (3.9)</td>
<td>45 (2.9)</td>
<td>1.0 (−0.2 to 2.3)</td>
<td>1.38 (0.93 to 2.04)</td>
<td>0.11</td>
</tr>
<tr>
<td>Lower-limb ischemia or amputation</td>
<td>4 (0.3)</td>
<td>7 (0.4)</td>
<td>−0.2 (−0.6 to 0.2)</td>
<td>0.57 (0.17 to 2.0)</td>
<td>0.38</td>
</tr>
<tr>
<td>Any skin problem</td>
<td>140 (9.0)</td>
<td>108 (6.9)</td>
<td>2.0 (0.1 to 3.9)</td>
<td>1.33 (1.03 to 1.73)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

IQR = interquartile range.
† Calculated by using the Mann–Whitney U test.

than is prophylaxis with thigh-length stockings. Skin problems were more frequent with thigh-length stockings, but these were usually mild. The groups did not differ in survival, calf DVT, pulmonary embolism, or adherence.

In November 2009, we performed an extensive literature search for a Cochrane review of randomized trials of stockings in patients with stroke, which involved searches of MEDLINE, Embase, and the Cochrane Stroke Groups Specialized Register of Trials (13). We pooled the results of CLOTS Trial 1 (thigh-length vs. no stockings) with those of the only other eligible trial (6), which yielded an OR of 0.88 (CI, 0.72 to 1.08) for all DVT events. To our knowledge, CLOTS Trial 2 is the only randomized trial to compare thigh-length and below-knee stockings in patients with stroke. We pooled the CLOTS Trial 2 results with data from 5 trials in a systematic review (14) that compared thigh-length and below-knee stockings in surgical patients. This yielded an OR for any DVT (proximal or distal) of 0.75 (CI, 0.59 to 0.95) in favor of thigh-length stockings. If thigh-length stockings are truly ineffective in patients with stroke, it may be surprising that they seem to be more effective than below-knee stockings. One explanation is that below-knee stockings may increase the risk for DVT after stroke. To explore this possibility, we performed an adjusted indirect comparison of below-knee and no stockings for the primary outcome in the CLOTS trials, using the method described by Glenny and colleagues (15). This yielded an OR of 0.71 (CI, 0.49 to 1.03), a trend toward fewer DVT events with no stockings compared with below-knee stockings. Another explanation is that the point estimate of the effect of thigh-length versus no stockings provided by CLOTS Trial 1 (OR, 0.98) was slightly pessimistic and that the true effect is closer to the lower boundary of the CI (OR, 0.76). We pooled the results of CLOTS Trials 1 and 2, assuming that below-knee stockings were equivalent to no stockings. The pooled estimate of effect of thigh-length versus no stockings or ineffective below-knee stockings was 0.82 (CI, 0.68 to 0.99; heterogeneity chi-square, 3.17; P = 0.075). If we assume that about 10% of patients develop proximal DVT after stroke, this translates into a number needed to treat to prevent 1 (most likely asymptomatic) proximal DVT event of about 60, whereas the number needed to harm to cause a skin break is only 35 (8).

In the CLOTS Trial 2, thigh-length stockings reduced proximal but not distal DVT. Could below-knee stockings reduce the risk for proximal DVT? If compression stockings work by reducing the cross-sectional area of the veins and thereby increasing the blood flow velocity, then below-knee stockings are unlikely to increase blood velocity in the proximal veins. However, most proximal DVT events are caused by the propagation of distal DVT (12), so preventing distal DVT should prevent proximal DVT.

Our broad eligibility criteria maximize the generalizability of our results, at least to the population with stroke. The patients were enrolled by 112 hospitals in 9 countries. Data from the Scottish Stroke Care Audit (National Report 2006, available at www.strokeaudit.scot.nhs.uk/) show that the average age of all persons hospitalized with acute stroke is 73 years (compared with 76 years in the CLOTS Trials), and about 60% are immobile and would have met our eligibility criteria. The low levels of prophylactic anticoagulation in our trial reflect the evidence-based national guidelines of the countries involved (16–20). However, the subgroup analyses do not suggest that the effects of stockings are materially different in patients who also receive anticoagulants (Figure 2), and therefore our results are probably applicable in countries where anticoagulants are used more frequently.

Our study has limitations. Blinding of the ultrasonographers was imperfect, which could have biased detection of our primary outcome, and assessment of some of the secondary outcomes could also be biased, because patients and caregivers could not be blinded. Our inability to perform all scheduled compression duplex ultrasonography, although unlikely to introduce bias, reduced the number of DVT events detected and therefore the power of our trial.
The CLOTS Trials may underestimate the clinical importance of the effects of stockings because we did not systematically screen for symptomatic DVT, many patients received anticoagulant therapy to lessen the risk for symptomatic events. Other limitations included lack of screening logs, early (but not data-dependent) cessation of recruitment on ethical grounds, and no central verification of negative results or 100% source data verification; however, these are unlikely to have introduced bias or altered the external validity of our results.

Our results have important implications for practice and research in patients with stroke. The results of the 2 completed CLOTS Trials suggest that thigh-length stockings are unlikely to have clinically important benefits for patients with stroke. Some clinicians hoped that below-knee stockings would be more effective than thigh-length stockings. The CLOTS Trial 2 results have shown that adherence to a regimen of below-knee stockings is not materially better than that for thigh-length stockings and that use of below-knee stockings is associated with a higher risk for DVT. With the ongoing CLOTS Trial 3, we aim to establish whether intermittent pneumatic compression offers an effective alternative to stockings for patients with stroke.

Our results might also have implications for other categories of hospitalized patients at risk for DVT, such as those undergoing elective surgery. Unfortunately, no randomized trials have compared below-knee stockings with no stockings. We have shown that thigh-length stockings are probably more effective than below-knee stockings. The 2.5-percentage point difference in absolute risk for proximal DVT may not seem to be of great clinical significance for individual patients (number needed to treat to prevent a proximal DVT, 40); however, many patients worldwide are fitted with stockings for DVT prophylaxis, which suggests a potentially substantial effect on public health. Most manufacturers recommend that physicians prescribe thigh-length stockings and reserve below-knee stockings for patients who cannot tolerate them. However, this recommendation is widely ignored: In Scotland, 74% of stockings purchased by the National Health Service in 2008 were below-knee stockings (G. Bowler, National Health Service Procurement. Personal communication), although whether the CLOTS Trial 2 results should be extrapolated to other patient groups is debatable, it would seem sensible that thigh-length stockings are both as effective as thigh-length stockings and more effective than no stockings.

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Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M10-1009.

Reproducible Research Statement: Study protocol: Available at www.clostrial.com. Statistical code: Available from Dr. Dennis (e-mail, martin.dennis@ed.ac.uk). Data set: Will be available via the open-access Edinburgh Data Repository after publication of the main papers.

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Final approval of the article: M. Dennis, P. Sandercock, J. Reid, C. Graham, G. Murray, G. Venables.
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Provision of study materials or patients: M. Dennis, J. Reid.
Statistical expertise: C. Graham, G. Murray.
Obtaining of funding: M. Dennis, P. Sandercock.
Critical revision of the article for important intellectual content: M. Dennis, P. Sandercock, A. Rudd, G. Bowler.
Collection and assembly of data: M. Dennis.

APPENDIX: MEMBERSHIP OF THE CLOTS TRIAL COLLABORATION

Trials Collaboration

Chief Investigator: M Dennis.
CLOTS Trial Coordinating Center: G Cranswick, A Deary, A Fraser, C Graham, S Grant, A Gunkel, J Hunter, A MacRae, D Perry, V Soosay, C Williams, A Williamson, A Young.

Writing Group: M Dennis (Chair), P Sandercock, J Reid, C Graham, G Murray, G Venables, A Rudd, G Bowler.

Trial Steering Committee: G Cranswick, M Dennis, C Graham, S Lewis, G Murray, J Reid, A Rudd, P Sandercock, G Venables (Chair), G Bowler, and observers from the Medical Research Council and Tyco Healthcare (Covidien).

National Coordinators: MG Celani, S Ricci (Italy); R Lindley (Australia).

Auditors and Translators: MG Celani (translation), M Hauvast (data audit), M Paterson (data audit), J Reid (audit of positive DVT evidence), T Ting (translation).


Participating Centers

We have listed each hospital with the names of the local principal investigator, local coordinator, and other significant contributors (in alphabetical order) who have enrolled patients into the CLOTS trials. The hospitals are grouped by country and ordered by the number recruited into CLOTS Trial 2. The figure in brackets represents number of patients recruited into CLOTS Trial 2. Centers listed as contributing zero patients only recruited patients into CLOTS Trial 1.

Australia (27 patients)
Royal Perth Hospital, Perth (26 patients): A Claxton, G Hankey.
St. George Hospital, Kogarah (1 patient): P Boers, R Millar.
John Hunter Hospital, New Lambton (0 patients): A Royan, M Russell.
Westmead Hospital, Westmead (0 patients): N Beydoun, R Lindley, M Romerosa.

Canada (16 patients)
Queen Elizabeth II Health Sciences Centre, Halifax Infirmary, Halifax (16 patients; CLOTS Lite): G Gubitz, J Jarrett, K Legg, M MacKay, S Nearing, S Phillips.

Czech Republic (9 patients)
District Hospital Pardubice, Pardubice (9 patients): E Ehler, P Geier, M Mrklovský.

India (33 patients)
St. John’s Medical College Hospital, Bangalore (33 patients; CLOTS Lite): AM Anandan, G Kusumakar, J Rosario, AK Roy.

Ireland (65 patients)
St. Vincent’s University Hospital, Dublin (35 patients): M Crowe, I Noone.
Midland Regional Hospital at Mullingar, Mullingar (30 patients): C Duffy, E Farrelly, M Jadrnickova, L Masterson, J Morris, S Murphy.

Italy (375 patients)
Università di Sassari, Sassari (37 patients): MA Fancellu, LD Parish, P Pileri, M Pinna, MP Piras, A Pirisi, C Scodino, ML Zedde.
Azienda Ospedaliera Sant’Andrea–Roma, Rome (18 patients): M Rasura.
Ospedale S. Giovanni Battista–Foligno Perugia, Perugia (7 patients): S Stefanucci.
San Matteo Degli Infermi–Spoleto, Spoleto (6 patients): GS Grasselli.
Ospedale Maggiore–Bologna, Bologna (0 patients): G Proccaccianti.
Ospedale A Segni, Ozieri (0 patients): P Beccu, A Del Rio, M Fresu, MA Musselli, A Pala, S Traccis.
Policlinico Universitario G. Martino, Messina (0 patients): MR Musolino.

Mexico (2 patients)
Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, Mexico City (2 patients; CLOTS Lite): A Leyva.

Portugal (49 patients)
Hospital de Santa Maria, Lisbon (49 patients; CLOTS Lite): P Canhão, F Falcão, TP Melo.

United Kingdom (2538 patients)
York Health Services National Health Service Trust, York (208 patients): J Coyle, C Croser, C Rhymes.
Barnsley District General Hospital, Barnsley (128 patients): MK Al Bazzaz, K Elliott, K Hawley, L Smith.
YeoVil District Hospital, Yeovil (122 patients): N Beacham, C Buckley, S Bulley, D Gibbons, L Jones, C Lawson, S More, K Rashed, S Savage.
University Hospital of North Staffordshire, Stoke-on-Trent (111 patients): R Miller, C Roffe.
Aberdeen Royal Infirmary, Aberdeen (99 patients): P Acheampong, M Bruce, MJ Macleod.
Birmingham Heartlands Hospital, Birmingham (66 patients): J McCormack, R Shinton.
Brighton and Sussex University Hospital National Health Service Trust, Haywards Heath (65 patients): K Ali, J Breeds, C Rajkumar, S Walker.
John Radcliffe Hospital, Oxford (65 patients): C Barker, A Buchan, A Flowers, R Hanna, J Hinkle, J Kennedy, G Littlejohn, C Mayell, A McCulloch, R Teal, H Tinamisan, S Webster, M Westwood.
Cumberland Infirmary, Carlisle (64 patients): P Davies, C Walker.
Bishop Auckland General Hospital, Bishop Auckland (63 patients): V Baliga, E Brown, L Burnside, S Clayton, A Mehrzad.
Nottingham City Hospital, Nottingham (56 patients): M Adrian, P Bath, J Clarke, F Hammonds.
Royal Cornwall Hospital, Truro (54 patients): K Adie, R Bland, G Courtald, F Harrington, A James, A Mate, C Schofield, C Wroath.
St. John's Hospital, Livingston (47 patients): P Bailey, DFrench, K Jackson, SG Ramsay, I Spence.
Royal Liverpool University Hospital, Liverpool (45 patients): G Fletcher, C Kearns, S Lohara.
Newham General Hospital, London (41 patients): K Darawil.
University Hospital North Durham, Durham (41 patients): E Brown, C Church, P Earnshaw, S Hunter, E Roberts.
Rotherham General Hospital, Rotherham (41 patients): C Draper, J Harris, J Okewara.
Southend University Hospital, Westcliff-on-Sea (40 patients): P Guylar, C Khuoge, A O'Brien.
King's College Hospital, London (40 patients): A Davis, M Fitzpatrick, L Kalra, R Pathansali, C Potter.
Countess of Chester Hospital, Chester (38 patients): G Abbott, K Chatterjee, C Kelly.
Arrooce Park Hospital, Liverpool (38 patients): H Aitken, J Barrett, V Gott, A Lenfestey, V Little, D Lowe, G Sangster, P Weir.
Stirling Royal Infirmary, Stirling (33 patients): R Dick, M MacLeod.
Lincoln County Hospital, Lincoln (29 patients): R Brown, S Leach.
Fairfield General Hospital, Bury (29 patients): A Bell, C Boyden, L Corrigan, C Curley, J Howard, K Kawafi.
Sunderland Royal Hospital, Sunderland (28 patients): H Brew, E Brown, C Church, P Earnshaw, J Foster, D Gulliver, D Hindmarsh, S Hunter, J O'Connell, M Redick, E Roberts.
Doncaster Royal Infirmary, Doncaster (28 patients): N Betts, DK Chadha, L Holford, J Sayles.
St. Mary's Hospital Newport, Isle of Wight, Newport (23 patients): E Hakim, U Sinclair.
Harrogate District Hospital, Harrogate (21 patients): S Boland, S Brotheridge, J Crabtree, C Hare, S Lee, J Strover, G Whil, White.
Derriford Hospital, Derriford (21 patients): C Brown, P Dobson, B Hyams, L March, A Mohd Nor.
University Hospital Aintree, Liverpool (21 patients): J Atherton, E Bacabac, R Durairaj, R Kumar, M Kuofali, H Martin, A Sharma, V Sutton.
St. Mary's Hospital London, London (20 patients): A Arumugam, J Chataway.
St. Helens and Knowsley Hospital, Prescot (19 patients): R Brown, S Dealing, D Meek, T Smith.
Bradford Teaching Hospitals National Health Service Foundation Trust, Bradford (18 patients): I Green, I Johnston, K Lomas, S Maguire, C Patterson, S Riley, S Williamson.
Morriston Hospital, Swansea (17 patients): L Dacey, R Narasatnasingam, M Wani.
Musgrove Park Hospital, Taunton (17 patients): J Ashcroft, L Cauldwell, M Farrar, S Gillam, M Hanley, M Hussain, R Larkham, R Norris.

Ulster Hospital, Belfast (16 patients): A McCorley, M Matthews, M Power, R Wright.

Macclesfield District General Hospital, Macclesfield (16 patients): L Butler, C Davison, M Fairhurst, M Horner, F Hussain, C Loughran, M Sein, D Walker.

Watford General Hospital, Watford (15 patients): M Cottle, D Collins, P Jacob.

Northern General Hospital, Sheffield (15 patients): G Dunn, A Jones.


University Hospital of Hartlepool, Hartlepool (13 patients): D Bruce, S Crawford.

Salford Royal Hospital Foundation National Health Service Trust, Salford (13 patients): J Barber, A Ingham, C Levick, B Simpson, J Stevens, L Swindells, P Tyrrell, J Wainwright, T Whittle.


Royal Preston Hospital, Preston (13 patients): S Duberley, S Punekar.


University Hospitals Coventry & Warwickshire National Health Service Trust, Coventry (12 patients): P Ray, S Thelwell.

The County Hospital, Hereford (11 patients): C Jenkins, J Powell, J Smith.

Norfolk and Norwich University Hospital, Norwich (11 patients): H Bennett, M Downing, R Fulcher, P McCarthy, K Metcalf, N Wyatt.

James Cook University Hospital, Middlesbrough (11 patients): A Atkinson, P Bond, D Broughton, I Tullo.

West Camberland Hospital, Whitehaven (10 patients): J Frazer, L Haslop, R Jolly, E Lavery, O Orugun, J Starkey, A Young.

Derbyshire Royal Infirmary, Derby (10 patients): N Brain, R Donnelley, P Gorman, K McLean, K Muhiddin, C Roe, F Ryan, N Palin, G Powell, R Wells, E Wright.


Airedale General Hospital, Keighley (10 patients): A Catto, D Karanwal, K Lindsay, S Mawer, C Orgles, K Smith, K Spence, M White, S Williamson.

Basingstoke & North Hampshire National Health Service Foundation Trust, Basingstoke (10 patients): E Giallombardo.

Queens Park Hospital Blackburn, Blackburn (9 patients): N Roberts.

Queen’s Hospital Burton, Burton upon Trent (9 patients): B Mherjee, P Tari.
South Tyneside General Hospital, South Shields (4 patients):JA Graham, J Scott.
Worcestershire Royal Hospital, Worcester (4 patients): K Law, P Sanmuganathan, E Stratford.
North Manchester General Hospital, Manchester (3 patients):U Ahmed, B Simpson.
Borders General Hospital, Melrose (3 patients): A Brown, S Haines, M Mckay, A McLaren, J Reid.
South Manchester University Hospitals National Health Service Trust, Manchester (3 patients): F Kelly, GE Gamble, SJ Welsh.
Belfast City Hospital, Belfast (3 patients): I Wiggam.
Lister Hospital, Stevenage (2 patients): L Butler, P Ghosh, C O’Brien.
University Hospital of North Tees, Stockton (1 patient): IM Anwar, S Crawford.
Stobhill National Health Service Trust, Glasgow (0 patients): P Fraser, R Graham, C McAlpine, M Shields.
St Thomas’ Hospital, London (0 patients): F Asare, H Audebert, S Banfield, J Birns, G Cluckie, N Iles, J Leon, A Reindorf, O Roncale, A Roots, R Sankoh, V Scott, N Smyth.
Derby City General Hospital, Derby (0 patients): K Muhideen, P Thornton.
Scarborough Hospital, Scarborough (0 patients): S Jamieson, J Paterson, R Rose.
Luton and Dunstable Hospital, Luton (0 patients): G Jutlla, S Ramkumar, L Sekaran, S Sethuraman.
Mid Staffordshire National Health Service Foundation Trust, Stafford (0 patients): B Clamp, A Oke.

Hexham General Hospital, Hexham (0 patients): J Robson, A Wright.
Raigmore Hospital, Inverness (0 patients): L Campbell, P Findlay.
Hemel Hempstead Hospital, Hemel Hempstead (0 patients): K Butchard, R Farag.
Salisbury District Hospital, Salisbury (0 patients): J Cronan, L Harris, D Walters.
William Harvey Hospital, Ashford (0 patients): L Cowie, DG Smithard.
Eastbourne District General Hospital, Eastbourne (0 patients): A Conrad, N Cornford, J Gallagher, F Kirrage, A Mason.
Queen Elizabeth Hospital, King’s Lynn (0 patients): A Lankester, J Phillips.
Western General Hospital, Edinburgh (0 patients): M Dennis, E Eadie, S Keir, L Smith, P Taylor, A Thomas, J Wardlaw.
Kent & Canterbury Hospital, Canterbury (0 patients): HS Baht, C Collins.
Lorn and Islands District General Hospital, Oban (0 patients): H Hamilton, F Johnson, S Reilly, K Smeaton.
Broomfield Hospital, Chelmsford (0 patients): J Blackwell, V Unachandran.
Hairmyres Hospital, East Kilbride (0 patients): M Dobbin, E Feeley, L Forsyth, F Gardner, B MacInnes, B Martin, C Stirling, B Yip.
Torbay Hospital, Torquay (0 patients): D Kelly, S Szabo.
Gloucestershire Royal Hospital, Gloucester (0 patients): V Cannon, T Chambers, D Dutta, K Harvey, V Wager, G Ward.