Deep vein thrombosis (DVT) and pulmonary embolism are common complications of admission to hospital after stroke. Up to 42% of patients hospitalized with stroke develop venous thromboembolism (VTE).1

The CLOTS (Clots in Legs Or sTockings after Stroke) trials assessed the effectiveness of graduated compression stockings (GCS) in stroke patients.2,3 The CLOTS Trial 1 compared thigh-length stockings versus no stockings in 2518 immobile, hospital-admitted stroke patients. Its primary results showed that compared with no stockings, thigh-length stockings were associated with a very small and statistically insignificant 5/1000 (95% confidence interval [CI], –19 to 29 reduction; \( P = 0.88 \)) reduction in the absolute risk of a symptomatic or asymptomatic proximal DVT within 30 days. The CLOTS Trial 2 showed that compared with below-knee stockings, use of thigh-length stockings was associated with a statistically significant absolute reduction in proximal DVT by 30 days in 25/1000 (95% CI, 7–44; \( P = 0.008 \)).

The appropriateness of focusing on DVT, including asymptomatic events identified on imaging, has been widely questioned.4 Although VTE prophylaxis aims primarily to reduce the frequency of fatal and nonfatal pulmonary emboli, these are relatively rare events that are difficult to confirm without screening with computerized tomography and routine autopsies among patients who die. In common with almost all previous randomized controlled trials of VTE prophylaxis, the primary outcome in the CLOTS trials was a cluster including both symptomatic and asymptomatic DVT. These events are more easily detected than pulmonary emboli, and are far more common, so that reasonable statistical power...
can be attained with more practical sample sizes. However, this primary outcome may fail to take sufficient account of the adverse effects of prophylaxis, for example, bleeding on anticoagulation, or skins breaks with GCS. In the CLOTS Trial 1, we showed that use of thigh-length GCS was associated with a statistically significant excess of 38/1000 skin breaks (95% CI, 25–52/1000; P<0.001).

Simply demonstrating that more VTE events are prevented than adverse events caused is not sufficient, as it assumes that VTE events and adverse events have equal impact on long-term outcomes. There is a case for randomized controlled trials of VTE prophylaxis to focus on more important outcomes such as survival, functional outcomes, and health-related quality of life. Although, the CLOTS trials were not originally powered to detect effects on these important outcomes, it is crucial that these data are made available to estimate the plausible size of any treatment effects, and so that they can be incorporated into future systematic reviews of the literature. For example, a systematic review of the effect of prophylactic anticoagulation in nonsurgical hospital admissions was able to include over 36,000 patients, but did not identify any significant reduction in mortality associated with VTE prophylaxis. Here, we present the long-term outcomes of the patients enrolled into CLOTS Trials 1 and 2.

Methods

The methods of the CLOTS trials have been described in detail elsewhere. In brief, CLOTS Trials 1 and 2 are a pair of trials that share the same eligibility, randomization (minimization with a random element), data collection, and follow-up systems. They both have a multicentre, parallel design with a centralized randomization system to allocate treatment with a 1:1 ratio, and which ensures allocation concealment. Patients were eligible for inclusion if they: were admitted to hospital within 1 week of an acute stroke (ischemic or hemorrhagic); could be enrolled between the day of admission (day 0) and day 3 in hospital; and were immobile (ie, unable to walk independently to the toilet). We excluded patients with subarachnoid hemorrhage and those with severe peripheral vascular disease, diabetic, or sensory neuropathy. Having obtained consent, the clinician entered the patient’s baseline data into our computerized central randomization service via a secure web interface or a touch–tone telephone system. The system applied minimization to allocate groups within centers for 4 prognostic factors: delay since stroke onset (day 0 or 1 versus day >1); stroke severity with a validated prognostic model; 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. Because simple minimization 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.

In CLOTS Trial 1 patients were allocated to either routine care plus thigh-length stockings or routine care alone, and CLOTS trial 2 to either routine care plus thigh-length stockings or routine care plus below-knee stockings. Nursing staff applied the allocated length and size of the T.E.D. Anti-embolism Stockings, based on the manufacturer’s (Covidien, MA) fitting instructions, to both legs that were then worn day and night until the patient was: independently mobile; discharged from the randomizing hospital; refused to wear stockings; or the staff became concerned about the patient’s skin. We stipulated that both treatment groups should receive the same routine care that could include, depending on local protocols, early mobilization, hydration, antiplatelet, or anticoagulant drugs, including unfractionated heparin or low molecular weight heparin.

The primary outcome was the occurrence of either asymptomatic DVT in the popliteal or femoral veins (detected on the first or second compression duplex ultrasound performed as part of the trial protocol) or symptomatic DVT in the popliteal or femoral veins, confirmed on imaging within 30 days of randomization. The secondary outcomes reported here were: survival, functional status, Oxford Handicap Scale (a version of the modified Rankin scale), and health-related quality of life (EQ5D-3 L) at 6 months, and occurrence of DVT or pulmonary emboli in the 6 months after randomization. The trial-coordinating center in each country obtained follow-up data on secondary outcomes by postal or telephone questionnaires to patients or carers, and also their family doctors about 6 months after randomization. Those carrying out telephone follow-up were unaware of treatment allocation or the occurrence of a primary outcome unless, during a telephone follow-up, the patients mentioned these.

Statistical Analysis

CLOTS Trials 1 and 2 were event-driven trials. The sample size and recruitment targets were specified in terms of the number of primary outcome events (ie, proximal DVTs within 30 days), and hence were not likely to be sufficient to demonstrate clinically valuable treatment effects on survival and functional status by 6 months. For the purposes of all analyses, we retained participants in the treatment group to which they were originally assigned. To compare categorical secondary outcomes, we calculated differences of proportions with 95% CIs, χ², and Fisher exact test. We compared survival in the treatment groups with Cox proportional hazard models censored at 6 months after randomization (thereafter, reporting of deaths was inconsistent), including the factors included in our minimization algorithm (ie, delay from stroke onset to randomization [Day 0–1 versus >1], ability of the patient to lift both legs off the bed, use of anticoagulants or alteplase, and predicted stroke outcome). Utilities derived from the EQ5D-3 L were compared with the Mann–Whitney U test.

For the purposes of these analyses, we excluded 100 patients enrolled in a substudy of CLOTS Trial 2, referred to as CLOTS-Lite, which had the same primary outcome, but did not follow patients beyond the first 30 days. The Multicentre Research Ethics Committees in the United Kingdom and the local ethics committees in all contributing centers approved our protocol. We obtained written informed consent from all patients, or for patients lacking mental capacity, from a valid proxy. The trial was registered (ISRCTN28163533).

Role of the Funding Sources

The sponsors of the study had no role in data collection, storage or analysis, drafting of this report, or the decision to publish. The corresponding author (M.D.) had full access to all the data in the study, and had final responsibility for the decision to submit for publication.

Results

We enrolled our first patient on March 7, 2001, and the last on May 28, 2009, and completed the follow-up in February 2010. The baseline characteristics, adherence to allocated treatment, and results with respect to our 30-day primary and secondary outcomes, and the short-term outcomes in our prespecified subgroups have been published elsewhere. The trial flow diagrams relevant to the current analyses are shown in Figure. In both trials, prophylactic dose unfractionated or low molecular weight heparin was used in only a minority of patients. In Trial 1, 117 (9.3%) of the 1256 allocated thigh-length GCS, and 129 (10.2%) of those allocated to avoid GCS received prophylactic anticoagulants in hospital after enrolment. In Trial 2, the proportions were 156 (10.1%) of 1552.
allocated thigh-length GCS and 175 (11.2%) of 1562 allocated below-knee GCS.2,3

Table 1 shows the proportions of patients in each treatment group who developed VTE events before their final follow-up, and any antithrombotic medication surviving patients were taking at final follow-up. There were no statistically significant differences in VTE events by 6 months between the treatment groups in either trial, even though there had been a small, but statistically significant, excess of proximal DVTs within 30 days with below-knee GCS in Trial 2.3

We compared survival in patients enrolled in Trials 1 and 2 with a Cox proportional hazards model, including the

Table 1. Antithrombotic Medication at Final Follow-Up and Venous Thromboembolic Events During 6-Month Follow-Up

<table>
<thead>
<tr>
<th>Medications</th>
<th>CLOTS Trial 1</th>
<th>CLOTS Trial 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Thigh-Length</td>
<td>No Stockings</td>
</tr>
<tr>
<td>Medications</td>
<td>n=1256 %</td>
<td>n=1262 %</td>
</tr>
<tr>
<td>Aspirin</td>
<td>589 46.9</td>
<td>601 47.6</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>224 17.8</td>
<td>223 17.7</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>75 6.0</td>
<td>77 6.1</td>
</tr>
<tr>
<td>Warfarin</td>
<td>195 15.5</td>
<td>210 16.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Events within 6 mo</th>
<th></th>
<th>P Value</th>
<th>Abs Diff %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(95% CI)</td>
<td></td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Dead by 6 mo</td>
<td>258 20.5</td>
<td>249 19.7</td>
<td>0.7</td>
<td>0.612</td>
</tr>
<tr>
<td>Any DVT (whole leg)</td>
<td>210 16.7</td>
<td>230 18.2</td>
<td>1.5</td>
<td>0.320</td>
</tr>
<tr>
<td>Deaths as a result of PE</td>
<td>5 0.4</td>
<td>9 0.7</td>
<td>0.3</td>
<td>0.278*</td>
</tr>
<tr>
<td>Any confirmed PE</td>
<td>25 2.0</td>
<td>33 2.6</td>
<td>0.6</td>
<td>0.296</td>
</tr>
<tr>
<td>Missing 6 mo outcome</td>
<td>7 0.6</td>
<td>7 0.6</td>
<td>0.0</td>
<td>1.00*</td>
</tr>
<tr>
<td>Alive but no 6 mo data</td>
<td>31 2.5</td>
<td>28 2.2</td>
<td>0.2</td>
<td>0.679</td>
</tr>
</tbody>
</table>

CLOTS indicates Clots in Legs Or sTockings after Stroke; DVT, deep vein thrombosis; and PE, pulmonary embolism.

*Fisher test.
variables included in our minimization algorithm. In both trials, allocation to thigh-length GCS was associated with a very slight, but nonsignificant, increased hazard of death in the first 6 months (Trial 1: hazard ratio, 1.087; 95% CI: 0.913–1.295; and Trial 2: HR, 1.037; 95% CI, 0.892–1.205).

Table 2 compares the proportions of patients in different Oxford Handicap Scale categories (0, no symptoms; 6, dead) at 6-month follow-up, and their median utility scores derived from the EQ5D-3 L in the different treatment groups. Again, there were no statistically significant differences between the treatment arms in either CLOTS Trial 1 or 2, despite the differences in frequency of skins breaks seen in Trial 1.

Of the 5532 patients in both trials combined, 494 (8.9%) had a proximal DVT, 816 (14.8%) any DVT, 288 (5.2%) a symptomatic DVT (proximal or distal), and 74 (1.3%) a pulmonary embolism confirmed on imaging or autopsy within 30 days. If one subtracts the numbers of VTE events during the first 30 days from the total numbers occurring by the 6-month outcome assessment (Table 1), then only 31 (0.56%) had a symptomatic DVT and 41 (0.74%) a pulmonary embolism between 30 days and 6 months.

Discussion
We have not shown any statistically, or clinically, significant effect of wearing thigh-length or below-knee GCS on rates of VTE events, survival, functional outcomes (Oxford Handicap Scale), quality of life (EQ5D-3 L), or living circumstances at 6 months. This is despite small, but statistically significant, differences in rates of skins breaks in CLOTS Trial 1\(^2\) and proximal DVT in CLOTS Trial 2.\(^3\)

We have demonstrated that the risk of DVT and pulmonary emboli is much higher in the first month after stroke, than in the subsequent 5 months. It seems appropriate therefore to concentrate any efforts to reduce the risk of VTE in the first month after stroke.

The only other published randomized trial of GCS in stroke patients identified by a recent Cochrane review did not report any outcomes beyond the initial hospital admission.\(^9,10\) The CLOTS trials were not powered to identify differences in Oxford Handicap Scale or EQ5D-3 L at 6 months—so could have missed a small treatment effect. However, we can fairly confidently exclude a >10% relative reduction in mortality associated with use of thigh-length GCS. Possible explanations for the lack of observed effect which have been discussed previously,\(^2,3\) other than simply that GCS are ineffective, include: delays in applying the interventions so that DVTs had already formed before treatment; incorrect application of the GCS associated with the complexities of the sizing regime; suboptimal adherence because of patients and staff choosing to remove GCS early.

In summary, the CLOTS trials have not provided evidence of overall benefit or harm from the use of GCS after stroke, although the CIs around our estimates of treatment effects do not exclude the possibility of clinically relevant effects, either beneficial or harmful, on long-term outcomes.
Acknowledgments
The membership of the CLOTS trial collaboration has been detailed in previous publications.2,3 The CLOTS Trials were funded by research grants from the Chief Scientist Office of the Scottish Government, Chest Heart and Stroke Scotland and the Medical Research Council of the UK. Covidien provided the centers with supplies of T.E.D. Anti-embolism Stockings.

Disclosures
The authors have no financial or nonfinancial interests relevant to the submitted work except that Covidien provided free supplies of their graduated compression stockings to hospitals participating in the trials.

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The Effect of Graduated Compression Stockings on Long-term Outcomes After Stroke: The CLOTs Trials 1 and 2

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