Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial

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

Summary

Background **Venous thromboembolism is a common, potentially avoidable cause of death and morbidity in patients in hospital, including those with stroke. In surgical patients, intermittent pneumatic compression (IPC) reduces the risk of deep vein thrombosis (DVT), but no reliable evidence exists about its effectiveness in patients who have had a stroke. We assessed the effectiveness of IPC to reduce the risk of DVT in patients who have had a stroke.**

Methods **The CLOTS 3 trial is a multicentre parallel group randomised trial assessing IPC in immobile patients (ie, who cannot walk to the toilet without the help of another person) with acute stroke. We enrolled patients from day 0 to day 3 of admission and allocated them via a central randomisation system (ratio 1:1) to receive either IPC or no IPC. A technician who was masked to treatment allocation did a compression duplex ultrasound (CDU) of both legs at 7–10 days and, wherever practical, at 25–30 days after enrolment. Caregivers and patients were not masked to treatment assignment. Patients were followed up for 6 months to determine survival and later symptomatic venous thromboembolism. The primary outcome was a DVT in the proximal veins detected on a screening CDU or any symptomatic DVT in the proximal veins, confirmed on imaging, within 30 days of randomisation. Patients were analysed according to their treatment allocation. Trial registration: ISRCTN93529999.**

Findings **Between Dec 8, 2008, and Sept 6, 2012, 2876 patients were enrolled in 94 centres in the UK. The included patients were broadly representative of immobile stroke patients admitted to hospital and had a median age of 76 years (IQR 67–84). The primary outcome occurred in 122 (8·5%) of 1438 patients allocated IPC and 174 (12·1%) of 1438 patients allocated no IPC; an absolute reduction in risk of 3·6% (95% CI 1·4–5·8). Excluding the 323 patients who died before any primary outcome and 41 without any screening CDU, the adjusted OR for the comparison of 122 of 1267 patients *vs* 174 of 1245 patients was 0·65 (95% CI 0·51–0·84; p=0·001). Deaths in the treatment period occurred in 156 (11%) patients allocated IPC and 189 (13%) patients allocated no IPC; died within the 30 days of treatment period (p=0·057); skin breaks on the legs were reported in 44 (3%) patients allocated IPC and in 20 (1%) patients allocated no IPC (p=0·002); falls with injury were reported in 33 (2%) patients in the IPC group and in 24 (2%) patients in the no-IPC group (p=0·221).**

Interpretation **IPC is an effective method of reducing the risk of DVT and possibly improving survival in a wide variety of patients who are immobile after stroke.**

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*See appendix for membership and contributions

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See Online for appendix

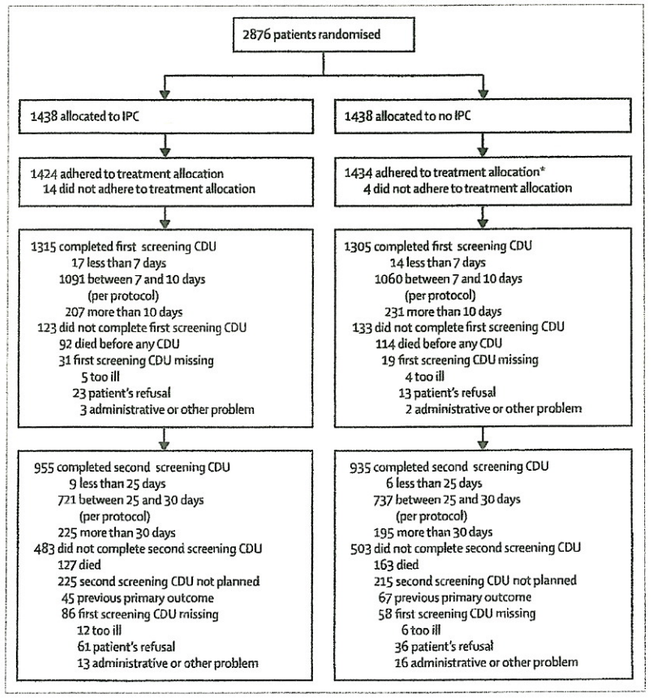

Figure 2: **Trial profile**
CDU=compression duplex ultrasound. IPC=intermittent pneumatic compression. *Four patients allocated avoid IPC received some IPC: three were transferred to an intensive therapy unit or high dependency unit where IPC was standard of care; the other patient received IPC because of miscommunication of the treatment allocation, which resulted in 3 days' treatment with IPC.

	IPC (n=1438)	No IPC (n=1438)
Age (years)		
Median (IQR)*	76 (67–83)	77 (68–84)
Mean age (SD)	74·2 (12·3)	74·9 (11·9)
Sex		
Male	695 (48%)	688 (48%)
Final diagnosis at hospital discharge		
Stroke or TIA (definite or probably ischaemic)	1211 (84%)	1217 (85%)
Confirmed haemorrhagic stroke	187 (13%)	189 (13%)
Unknown type	19 (1%)	14 (1%)
Non strokes (included in primary analysis)	19 (1%)	18 (1%)
Missing (no discharge form)	2 (<1%)	0
Past history and risk factors		
Previous deep vein thrombosis or pulmonary embolism	66 (5%)	74 (5%)
Diabetes mellitus	256 (18%)	247 (17%)
Peripheral vascular disease	24 (2%)	31 (2%)
Overweight	417 (29%)	457 (32%)
Current cigarette smoker	250 (17%)	228 (16%)
Independent in daily activities before stroke*	1301 (90%)	1295 (90%)
Lives alone before stroke*	500 (35%)	503 (35%)
Indicators of stroke severity		
Able to lift both arms off bed*	499 (35%)	502 (35%)
Able to talk and orientated in time, place, and person*	886 (62%)	845 (59%)
Able to lift both legs off bed†	494 (34%)	493 (34%)
Able to walk without help*	0	0
Stroke severity—probability of being alive and independent in daily activities=0–0·15)†	898 (62%)	892 (62%)
Stroke severity—median (IQR) probability of being alive and independent in daily activities	0·09 (0·02–0·31)	0·09 (0·01–0·31)
On warfarin at recruitment	25 (2%)	29 (2%)
On heparin at recruitment	86 (6%)	78 (5%)
Taken aspirin, dipyridamole, or clopidogrel in past 24 h at recruitment	970 (67%)	971 (68%)
Received thrombolysis since admission	249 (17%)	255 (18%)
On heparin or warfarin at recruitment or received thrombolysis since admission†	347 (24%)	352 (24%)
Delay		
Delay since stroke onset to randomisation=0–1 days†	624 (43%)	620 (43%)
Delay since stroke onset to randomisation=2 days†	478 (33%)	457 (32%)
Delay since stroke onset to randomisation ≥3 days†	336 (23%)	361 (25%)
Compression duplex ultrasound at 25–30 days deemed unlikely to be practical at time of randomisation	225 (16%)	215 (15%)

Data are number of patients (%) unless otherwise stated. IPC=intermittent pneumatic compression. TIA=transient ischaemic attack. *Factors included in model to predict probability of being alive and independent at 6 months.[16] †Variables included in minimisation.

Table 1: **Baseline characteristics of patients enrolled into the CLOTS 3 trial (N=2876)**

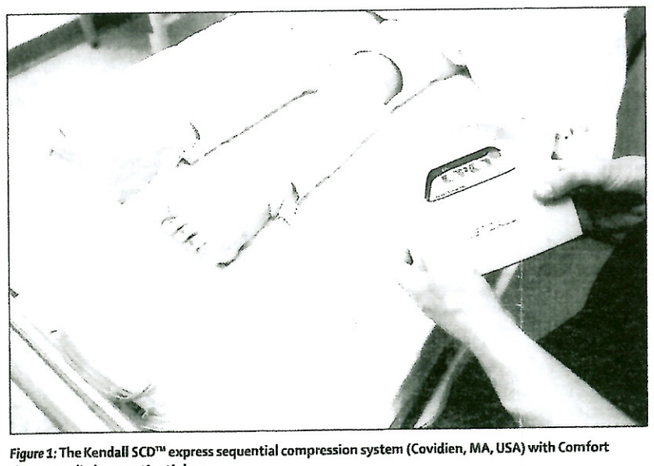

Figure 1: **The Kendall SCD™ express sequential compression system (Covidien, MA, USA) with Comfort sleeves applied to a patient's legs**

	IPC group	No IPC group
30-day clinical outcomes and background treatment		
Discharge form received (after hospital discharge or death)	1436 (99·9%)	1438 (100%)
Vital status at 30 days known	1432	1431
Post-randomisation prophylactic dose heparin/LMWH prescribed	248 (17%)	240 (17%)
Post-randomisation treatment dose heparin/LMWH prescribed	182 (13%)	219 (15%)
Graduated compression stockings worn	118 (8%)	42 (3%)
Thigh-length stockings only	90 (6%)	22 (2%)
Below-knee graduated compression stockings worn only	17 (1%)	19 (1%)
Both long and short worn	10 (<1%)	1 (<1%)
Unknown length	1 (<1%)	0
6-month clinical outcomes		
Patient or proxy withdrew consent before 6 months	13 (<1%)	7 (<1%)
Missing 6 month follow-up	10 (<1%)	13 (<1%)
No follow-up form because patient dead	330 (23%)	367 (26%)
Follow-up form received	1098 (76%)	1058 (74%)

IPC=intermittent pneumatic compression. LMWH=low-molecular-weight heparin.

Table 2: **Patients' clinical outcomes**