Which stroke patients gain most from intermittent pneumatic compression

Which stroke patients gain most from intermittent pneumatic compression: further analyses of the CLOTS 3 trial

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Background **The CLOTS 3 trial showed that intermittent pneumatic compression (IPC) reduced the risk of DVT and improved survival after stroke.**

Aims **To provide additional information which may help clinicians target IPC on the most appropriate patients by exploring the variation in its effects on subgroups defined by predicted prognosis.**

Methods **A multicentre, parallel group, randomized trial enrolled immobile acute stroke patients and allocated them to IPC or no IPC. The primary outcome was proximal DVT at 30 days. Secondary outcomes at six-months included survival, disability, quality of life, and hospital costs. We stratified patients into quintiles according to their predicted prognosis at randomization, based on the Six Simple Variable model.**

Results **Between December 2008 and September 2012, we enrolled 2876 patients in 94 UK hospitals. Patients with the best predicted outcome had the lowest absolute risk of proximal DVT (6·7%) and death by six-months (9·3%). Allocation to IPC had little effect on DVT, survival, disability, quality of life, hospital length of stay, or costs. In patients with the worst predicted outcomes, the overall risk of DVT and death was 16·0% and 51·3%, respectively. IPC reduced DVT (odds reduction 34%) and improved survival 17% and significantly increased length of stay and hospital costs. In the three intermediate quintiles, IPC reduced the odds of DVT (35–43%) and improved survival (11–13%). Disability and quality of life at six-months depended on baseline severity but was not influenced significantly by IPC.**

Conclusions **IPC appears to reduce the risk of DVT and probably improves survival in all immobile stroke patients, other than the fifth with the best prognosis. It therefore seems reasonable to recommend that IPC should be considered in all immobile stroke patients, but that the final decision should be based on a judgment about the individual's prognosis. In some, their prognosis for survival with an acceptable quality of life will be so poor that use of IPC might be considered futile, while at the other end of the spectrum, patients' risk of DVT, and of dying from VTE, may not be high enough to justify the modest cost and inconvenience of IPC use.**

Key words: DVT, prophylaxis, stroke, venous thromboembolism

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A full description of the trial will be published in the Health Technology Assessment journal series. Visit the HTA program website for more details: http://www.hta.ac.uk/project/2231.asp/. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health or Chief Scientist Office of the Scottish Government.

The CLOTS (Clots in Legs Or sTockings after Stroke) Trials Collaboration (see Appendix S1 for membership and contributions).

Subject code: [74] Other Stroke Treatment – Medical.

[†]See Appendix S1.

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Introduction

Venous thromboembolism (VTE) is common after stroke, causes significant morbidity, may delay hospital discharge, increases healthcare costs, and has been estimated to account for up to a quarter of all deaths after stroke (1). The CLOTS 3 trial showed that intermittent pneumatic compression (IPC) applied to the legs of immobile acute stroke patients reduces the odds of proximal DVT by about a third and improves survival over the first six-months (hazard ratio = 0·86; 95% CI 0·73–0·99 $P = 0·042$) (2). However, there were no significant differences between the treatment and control groups in disability, living circumstances, quality of life, or hospital costs (3). Based on these data, IPC has been recommended in clinical guidelines (4) and is being widely

implemented in stroke units throughout the United Kingdom (5). However, those writing these guidelines questioned whether IPC should be targeted on specific groups of immobile stroke patients.

It has been suggested that trialists should report the heterogeneity of treatment effects in groups defined by more than one characteristic as a way of providing decision makers with information which might inform their decisions about which patients are most likely to benefit from an intervention (6). We aimed to establish whether there were categories of immobile stroke patients, based on their predicted prognosis which takes account of six variables at baseline, who may potentially gain more or less from IPC, and in whom IPC might be more or less cost-effective.

Methods

The trial methods have been described in detail elsewhere (2,3,7,8). In brief, the CLOTS 3 trial used a multicentre, parallel group design with a centralized randomization system to allocate treatment with a 1 : 1 ratio, and which ensured allocation concealment. It enrolled consenting patients in 94 centers in the United Kingdom, from Day 0 to 3 of admission, and allocated them to IPC or no IPC on a background of routine care.

Between December 2008 and September 2012, we enrolled 2876 patients and completed follow-up in March 2013. Patients were eligible for inclusion if they: were admitted to hospital within three-days of an acute stroke (ischemic or hemorrhagic); could be enrolled between the day of admission (day zero) and day 3 in hospital; and were immobile (i.e. unable to walk independently to the toilet). We excluded patients with subarachnoid haemorrhage and those with severe peripheral vascular disease, congestive heart failure, or skin lesions on the legs which are considered to be contraindications to IPC.

Having obtained consent, the clinician entered the patient's baseline data into a computerized central randomization service via a secure web interface. Once the computer program had checked these baseline data for completeness and consistency, it generated that patient's treatment allocation – either 'routine care plus IPC' or 'routine care and no IPC'. A minimization algorithm was used which included four variables: predicted stroke outcome, delay from stroke onset to randomization, ability of the patient to lift both legs off the bed, and use of anticoagulants or alteplase. The patient's probability of achieving a good outcome [Oxford handicap scale (OHS) 0–2] was derived from the Six Simple Variable (SSV) model which has been extensively tested and validated in different cohorts (9,10). This includes the following variables:

- age
- prestroke independence in activities of daily living
- living alone at the time of the stroke
- ability to lift both arms off the bed
- ability to walk without help of another person (in this trial, no patient could walk independently), and
- ability to talk and not to be confused (i.e. normal verbal component of the Glasgow coma scale)

In patients allocated IPC, nursing staff applied the Kendall™ SCD express sequential compression system (Covidien, MA, USA) with thigh-length sleeves to both legs, according to the manufacturer's instructions,. The sleeves were to be worn day and night for 30 days or until: a second screening compression duplex ultrasound (CDU) had been performed (if after 30 days); the patient was independently mobile, discharged from the randomizing hospital, refused to wear the sleeves, or the staff became concerned about the patient's skin.

The primary outcome was the occurrence of a symptomatic or asymptomatic proximal DVT confirmed on CDU within 30 days of randomization. Secondary outcomes included: survival to six-months; disability (OHS (11)); quality of life (utilities based on EQ5D-3L (12)); and hospital costs (based on cost of IPC and length of hospital stay).

We estimated we would need 2800 patients to provide 90% power (alpha 0·05) to identify a 4% absolute reduction in our primary outcome (i.e. from 12% to 8%). For the purposes of all analyses, we retained participants in the treatment group to which they were originally assigned. We compared the proportions with primary or secondary outcome events with odds ratios and 95% confidence intervals (CIs). Survival was analyzed with a Cox model, and the OHS at final follow-up was analyzed as an ordinal scale by ordinal regression. All analyses were adjusted for the four variables included in our minimization algorithm. The health-related quality of life measured by the EQ5D–3L was converted into a utility based on UK population preferences (13) on a range of 1·0 (perfect health) to –0·5 (worst possible health). In this setting, the range of utility values account for health states worse than death.

The health economic methods have been described previously (3). The costs took account of hospital length of stay as well as the direct costs of IPC capital and equipment. Length of stay distributions were converted into cost estimates based on a per-diem hospital cost. Trial center/region-specific per-diem hospital costs were based on NHS reference costs in England and cost information for NHS Scotland derived from the Scottish Health Service Costs resource (14,15). We only had data on survival to six-months, so no reliable estimate of cost/QALY could be generated.

For these post hoc exploratory analyses, we divided the patients into quintiles (Quintile 1 lowest probability/worst prognosis to 5 highest probability/best prognosis) based on their predicted probability of having a good outcome at about six-months derived from the baseline (prerandomization) measurement of the SSV variables.

The protocol was approved by the Scotland A Multicentre Research Ethics Committee (08/MREC00/73) & the Newcastle & North Tyneside 1 Research Ethics Committee for England (08/H0906/137). The study was jointly sponsored by University of Edinburgh and NHS Lothian. The study is registered: http://www.controlled-trials.com/ISRCTN93529999.

The funders of the study, including Covidien, had no role in study design, data collection, storage, analysis or interpretation, drafting of this report, or the decision to publish. All of the named authors had full access to all data in the study and had final responsibility to submit for publication.

Results

The number of patients and the characteristics of the patients in each quintile are shown in Table 1. The absolute risk and the effect of IPC on the incidence of proximal DVT within 30 days (primary outcome), deaths at six-months, survival to six-months, quality adjusted survival, length of stay and hospital costs in each quintile, and overall are shown in Table 2. While there is no statistically significant heterogeneity across the groups, some patterns do emerge. The risk of proximal DVT was similar across quintiles 1–4 but lower in the mildest quintile. With IPC, there is a similar odds reduction in DVT (34– 43%) and absolute risk reduction (4·6–5·8%) in all quintiles apart from quintile 5 (mildest) where there was little evidence of an effect (7% and 0·5%, respectively). The risk of dying by six-months was highest in quintile 5 (52%) and gradually reduced across the quintiles to about 10%, confirming the predictive power of the SSV. Both the relative improvement in survival (17%) and absolute reduction in death (7·3%) with IPC was highest in quintile 1. However, there were smaller improvements in survival in quintiles 4-2 (11–13%) but worse survival (+40%) and higher absolute risk of death (2·1%) with IPC in the mildest quintile. There was no statistically significant gain in quality adjusted survival in the trial overall or any quintile. Figure 1 illustrates that the functional outcomes of patients improve as one moves from Quintile 1 (severest) to quintile 5 (mildest), confirming again the predictive value of the SSV. Using an ordinal regression analysis adjusted for baseline variables, there were no statistically significant treatment differences in the distribution of OHS between those treated with IPC and the untreated group, either overall or within any quintile. Overall, the length of hospital stay was longer in the IPC group than the control group, but this was most marked (6·8 days) and was statistically significant in the severest quintile. Length of stay is the main driver for hospital costs in the United Kingdom, which explains the greater excess cost of hospital care associated with allocation to IPC. This was largest and statistically significant in severest quintile. The increased length of stay probably reflects the improved survival.

Discussion

These further exploratory analyses suggest that patients in the quintile with the highest probability of a good outcome may gain little from IPC. Although IPC was associated with worse survival in this group, it seem highly likely, given the wide CIs that this observation was spurious. Furthermore, it appears that in patients with the lowest probability of a good outcome, IPC has the largest relative and absolute benefits on DVT and survival. The latter may explain why IPC use is associated with a greater increase in length of hospital stay and thus costs in the severest patients. The lack of obvious benefits in the mildest group may arise because that group have the lowest absolute risks of DVT and of dying within six-months. It seems likely that deaths due to VTE, which are the ones most likely to be reduced by IPC, will be uncommon in this group.

There was a suggestion, based on the average effect of IPC across all patient groups, that any improvement in survival may be at the expense of patients surviving with severe disability (3,16). These further, albeit post hoc and exploratory analyses, provide some reassurance that while this may be true for the severest patients, immobile stroke patients of intermediate prognosis may still gain from IPC in terms of avoidance of DVT and improved survival and with more acceptable functional outcomes and probably less associated increase in overall hospital costs.

These analyses show that the overall outcomes in both treatment groups improve as one moves from the severest to mildest quintile (Fig. 1), indicating that the SSV successfully stratifies

Table 1 Baseline characteristics of patients in each quintile defined by baseline prognosis derived from the Six Simple Variable (SSV) model

Quintile	1 (severest)	2	3	4	5 (mildest)	All
Probability of OHS 0-2 at 6 months	<0·01	0·01 to <0·046	0·046 to <0·13	0·13 to <0·396	0·396 to <1	
Number per group	537	585	592	577	585	2876
Mean (SD) age	84·6 (7·3)	75·2 (10·1)	76·6 (9·1)	68·9 (12·7)	68·1 (12·4)	74·5 (12·1)
Male (%)	164 (30·5)	270 (46·2)	281 (47·5)	301 (52·2)	367 (62·7)	1383 (48·1)
Independent before	331 (61·6)	538 (92·0)	566 (95·6)	576 (99·8)	585 (100)	2596 (90·3)
Living alone	319 (59·4)	161 (27·5)	242 (40·9)	187 (32·4)	94 (16·1)	1003 (34·9)
Prior VTE	23 (4·3)	26 (4·4)	40 (6·8)	22 (3·8)	29 (5·0)	140 (4·9)
Diabetes mellitus	86 (16·0)	107 (18·3)	99 (16·7)	96 (16·6)	115 (19·7)	503 (17·5)
Current Smoker	42 (7·8)	83 (14·2)	89 (15·0)	139 (24·1)	125 (21·4)	478 (16·6)
Obese	124 (23·1)	171 (29·2)	176 (29·7)	186 (32·2)	217 (37·1)	874 (30·4)
Talking normally	52 (9·7)	110 (18·8)	441 (74·5)	543 (94·1)	585 (100)	1731 (60·2)
Lift both arms	49 (9·1)	60 (10·3)	142 (24·0)	200 (34·7)	550 (94·0)	1001 (34·8)
Lift both legs	86 (16·0)	88 (15·0)	180 (30·4)	207 (35·9)	426 (72·8)	987 (34·2)
Lift one leg	363 (67·6)	420 (71·8)	393 (66·4)	363 (62·9)	154 (26·3)	1693 (58·9)
Lift neither leg	88 (16·4)	77 (13·2)	19 (3·2)	7 (1·2)	5 (0·9)	196 (6·8)
Able to walk	0	0	0	0	0	0
Intra cerebral haemorrhage	64/535 (12·0)	82 (14·0)	82 (13·9)	82 (14·2)	66 (11·3)	376/2874 (13·2)
Use of blood thinning agents (heparin, warfarin, thrombolysis)	100 (18·6)	152 (26·0)	123 (20·8)	164 (28·4)	160 (27·4)	699 (24·3)

The SSV variables are highlighted in grey.

Table 2 Effect of IPC on proximal DVT within 30 days (primary outcome): survival, quality-adjusted life years, length of hospital stay and costs of hospital care in each quintile defined by baseline prognosis derived from the SSV

Effects of IPC		Quintile 1: severest	Quintile 2	Quintile 3	Quintile 4	Quintile 5: mildest	All
n		537	585	592	577	585	2876
Proximal DVT	IPC	24/185 (13·0)	28/256 (10·9)	24/285 (8·4)	28/262 (10·7)	18/279 (6·5)	122/1267 (9·6)
n/N (%) (excluding dead and missing)	No IPC	39/208 (18·8)	37/239 (15·5)	35/252 (13·9)	44/273 (16·1)	19/273 (7·0)	174/1245 (14·0)
Odds reduction in DVT (95% CI)*		35% (–14 to 62)	34% (–13 to 61)	**43% (1–67)**	**41% (2–65)**	7% (–82 to 52)	**35% (16–49)**
Dead by six-months *n/N* (%)†	IPC	117/247 (47·4)	83/299 (27·8)	61/309 (19·7)	26/283 (9·2)	31/293 (11·1)	320/1436 (22·3)
	No IPC	158/289 (54·7)	88/286 (30·8)	61/283 (21·6)	31/293 (10·6)	23/287 (8·0)	361/1438 (25·1)
Reduction in hazard of death over six-months (95% CI)‡		17% (–6 to 34)	13% (–18 to 35)	11% (–27 to 38)	13% (–46 to 49)	–40% (–140 to 17)	**14% (1–26)**
Gain in quality-adjusted survival (year) within six-months (95% CI)		0·006 (–0·006 to 0·018)	0·008 (–0·007 to 0·024)	0·000 (–0·017 to 0·017)	–0·004 (–0·022 to 0·013)	–0·004 (–0·021 to 0·014)	0·003 (–0·005 to 0·011)
Mean increase in length of stay (days) (95% CI)		**6·8 (0·1, 14·5)**	1·0 (–6·2, 8·2)	3·2 (–1·0, 9·8)	–3·2 (–9·0, 2·5)	–0·3 (–4·6, 3·9)	1·6 (–1·5, 4·3)
Additional cost (£) of hospital care with IPC (95% CI)		**1537 (89–2986)**	467 (–1119 to 2053)	1022 (–164 to 2208)	–642 (–1906 to 622)	–25 (–949 to 936)	520 (–68 to 1108)

*Logistic regression adjusted for baseline variables and excluding death and missing patients. †The number of deaths at six-months is not the same as the number dead on OHS at final follow-up because some patients die after six-months and before the final follow-up is attempted. ‡Cox proportional hazards model adjusting for baseline variables. Results in bold are statistically significant at $P < 0.05$ level.

patients by predicted prognosis. In the severest group (quintile 1), the great majority of patients are either dead or very severely disabled. Nonetheless, even in this group, some patients may have a good outcome, and in the mildest group (quintile 5), some patients have poor outcomes. This may reflect not only a lack of discrimination in the model but also some variability in the scoring of the OHS by patients and carers, and the fact that some patients, even with mild strokes, have poorer outcomes than expected because they suffer recurrent strokes or develop other severe co-morbidity.

The CLOTS 3 trial had some important limitations relevant to these results. The trial was only powered to detect a 4% absolute reduction in the risk of proximal DVT within 30 days, but it lacked power to detect the improvements in survival, differences in the OHS, quality of life or costs overall, and certainly not in five subgroups. There was no statistically significant heterogeneity between the quintiles in respect to the outcomes assessed, so that any differences observed could have arisen due to the play of chance. Even statistically significant effects of IPC in a quintile may be spurious.

The lengths of stay and resulting costs of hospitalization are based on UK practice where rehabilitation is often completed as part of the initial acute hospital admission episode. In countries where acute hospital stays for stroke are much shorter, IPC may lead to greater use of rehabilitation facilities and/or community care rather than acute hospital resources.

Awareness of these further analyses may increase clinicians' confidence to select patients in whom IPC is likely to be both effective and cost-effective. IPC appears to reduce the risk of DVT and probably improves survival in all immobile stroke patients, other than perhaps the fifth with the best prognosis. It therefore seems reasonable to recommend that IPC should be considered in all immobile stroke patients but that the final decision should be based on a judgment about the individual's prognosis. In some, their prognosis for survival with an acceptable quality of life will be poor. In these patients, discussion with the patient or family to clarify the objectives of care may conclude that the use of IPC is futile. At the milder end of the 'severity' spectrum patients' risk of DVT, and of dying from VTE, may not be high enough to justify the modest cost and inconvenience of IPC use. These analyses suggest that 60–80% of immobile stroke admissions will potentially benefit from IPC.

Authors' contributions

M. D. was the chief investigator, designed the trial, was member of the steering committee, collected and verified data, and drafted this report. C. G. analyzed data and commented on drafts of this report. J. F. was involved in the design of the trial, participated in the steering committee, and with J. S. carried out the health economic analyses. Both commented on drafts of this paper. All members of the writing committee listed here have seen and approved the final version of the report. P. S. was involved in the design of the trial, participated in the steering committee, and commented on a draft of this report.

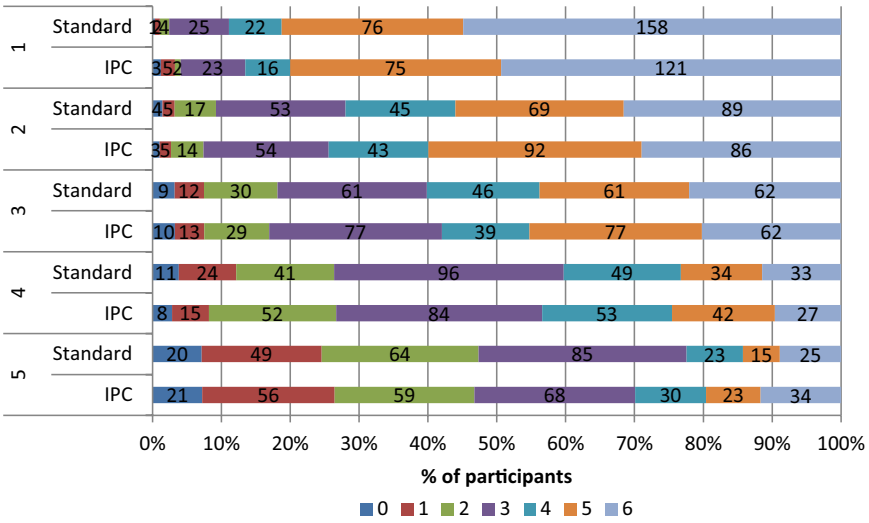

Fig. 1 The effect of IPC on disability (OHS) in each quintile. This shows the number and proportion of patients with an OHS of 0 (no symptoms), 1, 2, 3, 4, 5 (severe dependency), and 6 (dead) in each treatment group, in each quintile (quintile 1 severest – quintile 5 mildest). The patients with missing OHS data – IPC 17 (1·2%) and no IPC 18 (1·3%) are excluded.

Acknowledgement

See Appendix S1.

References

1 Kelly J, Rudd A, Lewis RR, Hunt BJ. Venous thromboembolism after acute stroke. *Stroke* 2001; **32:**262–7.
2 CLOTS (Clots in Legs Or sTockings after Stroke) Trials Collaboration. 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. *Lancet* 2013; **382:**516–24.
3 CLOTS (Clots in Legs Or sTockings after Stroke) Trials Collaboration. Effect of intermittent pneumatic compression on disability, living circumstances, quality of life and hospital costs after stroke: a randomised trial. *Lancet Neurol* 2014; **13:**1186–92.
4 Scottish Intercollegiate Guidelines Network. Management of patients with stroke. rehabilitation, prevention and management of complications and discharge planning. A national clinical guideline No. 118. 2010. http://www.sign.ac.uk (accessed 1 February 2015).
5 NHS Improving Quality. IPC Sleeves FAQ v1 29/05/2014. http://www.nhsiq.nhs.uk/media/2463598/ipc_sleeves_faqs_v1_290514.pdf (accessed 4 July 2014).
6 Kent DM, Rothwell PM, Ioannidis JPA, Altman DG, Hayward RA. Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal. *Trials* 2010; **11:**85.
7 Dennis M, Sandercock P, Reid J, Graham C, Forbes J. Does intermittent pneumatic compression reduce the risk of post stroke deep vein thrombosis? The CLOTS 3 trial: study protocol for a randomized controlled trial. *Trials* 2012; **13:**26.
8 Dennis M, Sandercock P, Murray G, Forbes J. Does intermittent pneumatic compression reduce the risk of post stroke deep vein thrombosis? The CLOTS 3 trial: statistical analysis plan. *Trials* 2013; **14:**66.
9 Counsell C, Dennis M, McDowall M, Warlow C. Predicting outcome after acute stroke: development and validation of new models. *Stroke* 2002; **33:**1041–7.
10 Teale EA, Forster A, Munyombwe T, Young JB. A systematic review of case-mix adjustment models for stroke. *Clin Rehabil* 2012; **26:**771–86.
11 Bamford JM, Sandercock P, Warlow C, Slattery J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1989; **20:**828.
12 Dolan P, Gudex C, Kind P, Williams A. A Social Tariff for EuroQol: Results from a UK General Population Survey. York, University of York, 1995.
13 Szende A, Oppe M, Devlin N (eds). EQ-5D Value Sets: Inventory, Comparative Review and User Guide. Dordrecht, Springer, 2007.
14 Department for Health. NHS reference costs 2011–2012. 2013.
15 Information Services Division, NHS Scotland. Scottish health service costs. 2013.
16 Hankey GJ. Intermittent pneumatic compression after stroke. *Lancet Neurol* 2014; **13:**1163–5.

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Membership and roles within the CLOTS trial collaboration.