U-shaped or J-shaped association between outcome of acute stroke (defined as death or dependency) and on-treatment blood pressure change—ie, large decreases or increases in blood pressure were associated with worse outcomes of acute stroke, although cognitive outcomes were not assessed. In fact, in rare cases or very small trials of acute stroke caused by large vessel stenosis, in which acute cognitive deficits are due to regional hypoperfusion beyond the infarct, temporary blood pressure elevation (with fluids or pressors) has resulted in improvement in cognitive function. Such cases of large vessel stenosis might represent the low end of the J-shaped association—ie, patients who have a poor outcome with a reduction in blood pressure after acute stroke.

The absence of an identified link between blood pressure and cognition in the SPS3 trial has several possible explanations. The intervention might not have affected cognition because there was no significant reduction in subsequent stroke. Alternatively, the intervention might have been started too late—it might be necessary to treat blood pressure before clinically significant small vessel disease (before stroke) to prevent cognitive decline. Or, it might be too soon (ie, the follow-up too short) for effects on cognition to be identified. Neuroprotective effects of blood pressure lowering on cognitive function, especially in the context of small vessel disease, might only be realised many years from the start of the intervention. Finally, a J-shaped or U-shaped association between blood pressure change and cognition might be identified by additional analyses, although such associations are more likely to be identified after acute strokes caused by large vessel stenosis than after acute lacunar strokes (as investigated in SPS3).

Despite the negative results of this study, investigators should continue to measure cognitive outcomes of stroke, and continue to investigate positive long-term effects of lowering blood pressure, preferably before, but also after lacunar stroke.

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Intermittent pneumatic compression after stroke

Acute stroke often causes immobility, which predisposes to deep vein thrombosis and pulmonary embolism and these can be fatal or disabling. Low-dose subcutaneous anticoagulation with heparins and heparinoids reduces the risk of venous thromboembolism, but the benefit is offset by haemorrhagic complications. Even targeting anticoagulation to patients at high risk of venous thromboembolism and low risk of bleeding does not add value because patients at high risk of venous thromboembolism (eg, increased severity of stroke) are also at high risk of bleeding. Application of graduated compression stockings to the legs is a physical method for the prevention of deep vein thrombosis in patients undergoing surgery, but it was ineffective in immobile patients with acute stroke in the CLOTS (Clots in Legs Or Stocckings after Stroke) trials 1 and 2. Intermittent pneumatic compression (IPC) is another physical method for the prevention of deep vein thrombosis in patients undergoing surgery. In 2013, according to the results of the CLOTS 3 trial, IPC, through...
thigh-length sleeves worn on both legs for 30 days and nights, was also effective in immobile patients with acute stroke. In *The Lancet Neurology*, the CLOTS Trials Collaboration now reports the results of a prespecified follow-up analysis of important secondary outcomes of CLOTS 3.

In CLOTS 3, allocation to IPC was associated with a reduction in the primary outcome of proximal deep vein thrombosis within 30 days of randomisation by a third compared with no IPC (8.5% vs 12.1%; risk ratio [RR] 0.68, 95% CI 0.54–0.85) and a reduction in the important secondary outcome of symptomatic deep vein thrombosis by a quarter (4.6% vs 6.3%; 0.73, 0.53–0.99). Also, mortality was significantly lower at 6 months after randomisation in patients in the IPC group than in the no IPC group. Although the proportion of patients who had died at the 6 month follow-up was not significantly different between the treatment groups (IPC 23.2% vs no IPC 25.8%; p=0.12), the probability of death up to 6 months after randomisation was significantly lower in the IPC group according to the results of the Cox model survival analysis (hazard ratio 0.86, 95% CI 0.74–0.99; p=0.042). This apparent discrepancy in the mortality has confused some readers. However, the survival analysis is the key analysis because it is more sensitive to a small, yet real, treatment effect of IPC. For example, if all patients in CLOTS 3 are followed up for the next 50 years, the proportion of patients in each group who will have died will be 100%, suggesting that there is no difference in mortality between the treatment groups. Yet, according to the results of a survival analysis there will be a difference in the time to death.

After the publication of the primary results of CLOTS 3, IPC has been widely implemented in stroke units because clinicians, for the first time, have felt confident that they now have a safe strategy for the prevention of deep vein thrombosis after stroke. But does a reduction in deep vein thrombosis by a third and in death by a seventh with IPC translate into an improvement in other outcomes that arguably matter more to immobile patients with stroke and their families (ie, long-term disability, living circumstances, and quality of life) and more to hospital managers (ie, hospital costs)?

Although the CLOTS 3 was not powered to reliably identify or exclude differences in these secondary outcomes, the main clinical findings from the new secondary analyses are that IPC use reduces the risk of deep vein thrombosis and improves survival, but does not improve disability, likelihood of living at home, quality of life, or quality-adjusted life days over the first 6 months compared with no IPC use. A caveat to these results is that the utility values used to estimate quality of life and quality-adjusted life days were based on the preferences of stroke-free individuals in the UK and might, or might not, reflect the views of patients with stroke or their carers. The main economic results are that IPC use is not expensive (£64.10 per patient or £5.48 per day of treatment), but that it increases overall hospital costs by improving survival and thus increasing the duration of hospital stay.

In the IPC group, case fatality was reduced by 3% at 6 months compared with no IPC (23% vs 26%; p=0.12). It is presumed, but not reported, that the reduction in case fatality with IPC was due to a reduction in the risk of fatal pulmonary embolism. The survival advantage with IPC was offset, however, by a 4% absolute increase in patients severely disabled (Oxford Handicap Score 5) at 6 months compared with no IPC (22% vs 18%; p=0.013). This finding might be due to chance because it is the result of a post-hoc exploratory analysis. However, it could also be real because the patients who are likely to develop a deep vein thrombosis, and have their life saved by IPC, are also likely to be disabled should they survive; stroke severity is a predictor of both deep vein thrombosis and severe disability. If so, the situation is similar to that of decompressive hemicraniectomy for malignant middle-cerebral-artery infarction in patients older than 60 years, whereby early hemicraniectomy significantly increases the probability of survival but most survivors have substantial disability. Survival with substantial disability instead of death is an outcome that might be acceptable to some patients and carers whereas it might not be acceptable to others.

The CLOTS Trials Collaboration is to be congratulated for completing the long-term follow-up of enrolled patients beyond that required for the primary outcome. The results of this secondary analysis provide important contextual information that tempers the enthusiastic conclusions drawn from the results of the primary efficacy analysis and enrich the evidence base for deciding whether to use or not use IPC. On the one hand, IPC use is an affordable intervention that prevents deep vein thrombosis and saves lives in some immobile patients with stroke who are hospitalised in...
Huntington's disease is not new. Now, however, a years before the occurrence of motor symptoms in quantitative motor measures that have prognostic value. as imaging data and cognitive, behavioural, motor, and

Studying the course of Huntington’s disease offers the rare opportunity to examine changes in a neurodegenerative process, years or even decades before unequivocal symptoms enable the clinical diagnosis to be made. Studies such as PREDICT-HD, an analysis from which is reported by Jane Paulsen and colleagues in The Lancet Neurology, and TRACK-HD describe early predictors such as imaging data and cognitive, behavioural, motor, and quantitative motor measures that have prognostic value.

The description of neuropsychiatric changes many years before the occurrence of motor symptoms in Huntington’s disease is not new. Now, however, a very precise quantification of these changes, occurring 12–15 years before diagnosis, is possible. Paulsen and colleagues followed up 1078 individuals with the Huntington’s disease gene mutation for a mean of 5 years (up to a maximum of 12 years), and showed that the best predictors of diagnosis beyond that provided by age and mutation repeat length in the top three phenotypic domains were total motor score, putamen volume, and Stroop word test.

Advances in the understanding of the pathophysiology of the disease from research in animal models have led to various potential therapeutic approaches. For some of these approaches, the first steps from preclinical to clinical research have been taken.

Such developments raise several questions. What is the disease onset for Huntington’s disease? If a treatment becomes available in the future, when in the course of the disease should we start to use it? Currently, the diagnosis of manifest Huntington’s disease is based on the presence of unequivocal motor signs (99% or 100% confidence, ie a diagnostic confidence level [DCL] of 4, on the Unified Huntington’s Disease Rating Scale [UHDRS]). How can we define a 99–100% confidence in diagnosis in more detail? Is there a special cutoff value in the motor score of the UHDRS for the establishment of the diagnosis? TRACK-HD used the strict inclusion criterion of 5 or fewer points in this scale for inclusion of premanifest mutation carriers. After 1 year, a significant increase in this measure was noted, without any further increase in the subsequent years. PREDICT-HD used the classic DCL of 4 as a criterion, and participants who were diagnosed with Huntington’s disease had a mean UHDRS total motor score of 22 (SD 9) at the time of diagnosis. More interestingly, in PREDICT-HD, participants without the mutation were shown to have an age-dependent increase in the UHDRS total motor score, with a 99th