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25 mm Hg versus 35 mm Hg elastic compression stockings to prevent post-thrombotic syndrome after deep vein thrombosis (CELEST): a randomised, double-blind, non-inferiority trial

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Summary

Background The optimal strength of compression needed to prevent post-thrombotic syndrome (PTS) after a proximal deep vein thrombosis (DVT) is debated. We aimed to assess whether 25 mm Hg elastic compression stockings (ECS) are non-inferior to 35 mm Hg ECS in preventing PTS after a DVT.

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Methods In this multicentre, double-blind, non-inferiority, randomised controlled trial, we enrolled adults (≥ 18 years) with a first ipsilateral proximal DVT attending 46 French vascular medicine hospital departments or private practices. Participants were randomly allocated (1:1, stratified by centre, age, and sex; with varying block sizes of two and four) to wear 25 mm Hg or 35 mm Hg ECS for 2 years. The primary outcome was the cumulative rate of PTS 2 years after inclusion, defined by a Villalta scale (≥ 5). Efficacy was assessed by intention-to-treat and in eligible participants who had complete primary outcome data. A per-protocol analysis was also conducted among compliant patients as a secondary outcome measure. Safety was assessed in all participants who used ECS at least once, and for which we have at least some tolerance information during follow-up. The margin for non-inferiority was 12.5%. This study is registered with ClinicalTrials.gov, NCT01578122, and has been completed.

Findings Between June 28, 2012, and July 21, 2017, we enrolled 341 eligible participants who consented to randomisation. 233 (68%) were men and median age was 59 years (IQR 45–70). Collection of ethnicity and race as a routine research variable is not authorised in France. Median follow-up was 735 days (IQR 721–760). 249 (73%) had complete data at 2 years. For the primary analysis, 40 (31%) of 129 participants with complete data in the 25 mm Hg ECS group and 40 (33%) of 120 in the 35 mm Hg group had PTS (absolute difference -2.3% [90% CI -12.1 to 7.4], $p_{\text{non-inferiority}}=0.0062$; relative risk 0.93, 95% CI 0.65 to 1.33). Results remained similar after imputation of missing data in patients we were authorised to do so: the cumulative proportion of PTS was 45 (29%) of 154 in the 25 mm Hg ECS group versus 52 (35%) of 148 in the 35 mm Hg ECS group (relative risk 0.83, 95% CI 0.60 to 1.16). Absolute difference was -5.9% , (90% CI -14.7 to 2.9), $p=0.0003$ for non-inferiority. Adherence was optimal ($>80\%$) and modified GIRERD score of 0–2) for 75 (51%) of 146 patients assigned to 25 mm Hg ECS and for 56 (42%) of 134 patients assigned to 35 mm Hg ECS ($p=0.11$). Regarding major adverse events related to ECS, there were no between-group differences in rates of deep vein thrombosis (0 vs 1 [0.6%]), ipsilateral leg ulcer (0 vs 1 [0.6%]), infection (0 vs 0), or death (0 vs 0) between the 169 patients evaluated in the 25 mm Hg ECS group and the 159 patients in the 35 mm Hg ECS group. Two (1%) of 328 patients who ever wore ECS developed ECS-related serious adverse events, one distal DVT and one leg ulcer (both in the 35 mm Hg ECS group). In the 25 mm Hg group, 6 patients died, 14 had a venous thromboembolic recurrence (proximal DVT or pulmonary embolism), and 7 had a major bleed. In the 35 mm Hg group, 5 patients died, 10 had a venous thromboembolic recurrence (proximal DVT or pulmonary embolism), and 6 had a major bleed.

Interpretation Although we did not reach the prespecified sample size, our results suggest that 25 mm Hg ECS are non-inferior to 35 mm Hg ECS in preventing PTS. Larger more powerful studies are needed.

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Introduction

Post-thrombotic syndrome (PTS) refers to manifestations of chronic venous insufficiency secondary to an episode of deep vein thrombosis (DVT).¹ PTS is common and can affect up to 50% of patients after

proximal lower limb DVT (ie, involving popliteal or more proximal deep veins).² Moreover, PTS significantly impairs the patient's quality of life and imposes a substantial economic burden on both patients and society.³

Research in context

Evidence before this study

The 2008 American College of Chest Physicians guidelines recommended the use of 30–40 mm Hg elastic compression stockings (ECS) for 2 years to prevent post-thrombotic syndrome (PTS) after deep vein thrombosis (DVT). This recommendation was based on the results of two small monocentric open-label randomised control trials (RCTs) showing an approximately 50% risk reduction in PTS in patients wearing versus not wearing 30–40 mm Hg ECS after DVT. However, a survey that we did among French vascular medicine physicians in 2009 (published in 2012) revealed that most physicians (>65%) prescribed ECS of lower than the recommended strength (<30 mm Hg) to favour adherence, but without evidence that this choice was efficacious. A 2011, systematic review on MEDLINE and ClinicalTrials.gov (using the terms post-thrombotic syndrome, post-phlebotic syndrome, and compression) identified no past or ongoing studies assessing the efficacy of ECS less than 30 mm Hg in preventing PTS after a DVT. The review was updated in 2020. The present double-blind RCT (CELEST) started including patients in 2012, and aimed to assess whether lower strength ECS (ie, 25 mm Hg) are non-inferior to higher strength (ie, 35 mm Hg) ECS to prevent PTS after a DVT. Since then, some international guidelines (eg, *Chest-International Society on Thrombosis and Haemostasis*, the American Heart Association, and the American Society of Hematology) following the results of a large double-blind RCT (ie, SOX, n=806), no longer recommend ECS to prevent PTS after a DVT. Indeed, the SOX RCT did not show any benefit of 30–40 mm Hg ECS versus placebo-ECS, to prevent PTS (adjusted hazard ratio 1.13 [95% CI 0.73–1.76]). Notably, adherence to ECS was suboptimal in SOX (56% of patients reported using study ECS more than 3 days a week at 2 years). There is a debate as to whether historical open-label studies were positive because of a placebo effect or if the SOX

In the absence of an effective treatment for established PTS, its management is challenging and thus prevention after a DVT is key.⁴ Along with anticoagulant treatment that is primarily prescribed to prevent DVT extension, but is also effective in preventing PTS,⁵ elastic compression stockings (ECS) are commonly used.⁶ ECS were shown to reduce local inflammation, vein wall fibrosis, and to prompt clot resolution.^{2,7} They thus target the main PTS pathophysiological mechanisms of inflammation, venous reflux, and venous obstruction. Two randomised controlled trials (RCTs) showed that ECS, as compared with no ECS, halved the risk of developing PTS after DVT.^{8,9} However, although adherence to ECS was excellent (eg, >80% of study patients wore them daily) in these studies, adherence to ECS use is much lower in routine clinical practice (ie, about 50%).¹⁰ Similar low adherence was shown in the large SOX trial and could explain why this study did not find any benefit of ECS compared with

double-blind RCT was negative because of lack of adherence to study ECS. In routine clinical practice, recent surveys showed that, ECS are still extensively used in many parts of the world for PTS prevention. Only another double-blind study could indisputably answer that key (new) question of ECS efficacy. The CELEST study has the potential to provide important additional information on ECS efficacy.

Added value of this study

Our data suggest that low strength ECS are non-inferior to high strength ECS in preventing PTS at 2 years after a DVT and adherence is better. As low strength ECS are easier to put on than high strength ECS, they could be preferred for the average patient with DVT. Among patients optimally adherent to ECS, the seemingly lower rate of PTS among patients wearing high strength ECS suggests that ECS are likely to be effective in preventing PTS after DVT but less than previously thought and considering that the study was underpowered.

Implications of all the available evidence

Apart from one negative double-blind study, overall evidence suggests a beneficial effect of ECS in preventing PTS after DVT. On the basis of the results of the CELEST and CANANO studies, we believe use of 20–30 mm Hg below-knee ECS should be considered after a DVT as this type of ECS has been shown to be similarly effective as higher strength or above knee ECS and they are easier to put on and better tolerated. High-strength ECS might be preferable for patients at high risk of PTS and who are motivated and expected to be adherent. On the basis of the OCTAVIA and IDEAL-DVT studies, the duration of ECS therapy should be decided on an individual patient basis. In the absence of PTS, most, but not all, patients can safely stop ECS therapy before 2 years and as early as 6 months post-DVT. Further studies are needed to confirm our results and better identify the role and the strength of ECS for PTS prevention on an individual patient basis.

placebo ECS.¹¹ Unquestionably, adherence to wearing stockings constitutes a major limitation to the efficacy of ECS-based PTS prevention strategies. Two of the main reasons for non-adherence reported across studies were the difficulty to put on the stockings and discomfort when wearing them.^{10,12} Use of lower-strength ECS (<30 mm Hg) than that used in previous RCTs might therefore favour adherence,¹³ but their efficacy is unknown.

From this perspective, we conducted the CELEST study (Compression Elastique Evaluation du Syndrome post Thrombotique), a multicentre double-blind RCT⁷ which aimed to assess whether 25 mm Hg ECS are non-inferior to 35 mm Hg ECS in preventing PTS.

Methods

Study design and participants

We carried out a double-blinded non-inferiority RCT that included patients from 46 French hospital-based vascular

medicine departments and private practices. Investigators who were invited to participate were either members of the French Society of Vascular Medicine, the College Francais de Pathologie Vasculaire, the Association des Médecins Vasculaires Hospitaliers, or the French INNOVTE thrombosis research network.

Eligible participants were inpatient and out-patient adults (≥ 18 years) with a first, acute (≤ 8 days), symptomatic, proximal DVT in the leg ipsilateral to the qualifying DVT. Key non-inclusion criteria were contralateral acute proximal DVT, previous proximal DVT in the leg ipsilateral to the qualifying DVT, expected duration of anticoagulant treatment to be less than 3 months, any invasive early thrombus removal procedure, IVC filter, phlegmatia cerulea, and ipsilateral trophic disorder (Clinical Etiological Anatomical Pathophysiology classification >3), and a life expectancy of less than 24 months. Full details of the inclusion and non-inclusion criteria are provided in the appendix (pp 37–38). Written informed consent was obtained from all participating patients.

The protocol was approved by the South East II Ethics Committee (Lyon, France) on Nov 9, 2011 (number 2011-032). It was amended on April 4, 2012, to authorise patients with previous contralateral DVT and contralateral PTS to be included; on May 7, 2014, to offer a larger choice of colours of ECS and below knee ECS for both men and women; and on May 5, 2015, to extend the period of patient recruitment from 3 to 8 days post DVT diagnosis. The study protocol has been previously published and a full version is included in the online appendix (pp 111–138).⁷ We report our findings in accordance with the CONSORT statements.¹⁴

Randomisation and masking

Patients were randomly assigned (1:1) to study groups by a web-based randomisation system (Clininfo, Lyon, France), which ensured concealed allocation. Randomisation was stratified by centre, age, and sex; and used varying block sizes of two and four. Two pairs of 25 mm Hg or 35 mm Hg ECS were shipped to the patient within 10 days after randomisation. Treatment allocation was masked from patients, health-care providers, study personnel, and study statisticians. To assess masking, after the end of the study patients were asked to which treatment they believed they had been assigned to receive: 25 mm Hg ECS, 35 mm Hg ECS, or uncertain or unable to guess.

Procedures

Patients were randomly assigned to receive either 25 mm Hg custom-fitted ECS (ie, LEGGER 25 classic for men and ACTYS 25 for women) or 35 mm Hg custom-fitted ECS (ie, LEGGER 35 for men and ACTYS 35 for women). All study ECS were manufactured, by Laboratoires Innothera (Arcueil, France), for the purpose of the study without any label to ensure blinding. At the baseline visit patients were given commercialised ECS (ie, VARISMA Comfort Coton model, 20–36 mm Hg,

a different strength and type from the trial ECS) to be worn until they had received the trial ECS. Stockings were replaced every 3 months and more frequently if required. Patients could choose between thigh-length or knee-length ECS, as well as the colour and open- or closed-toe models. Donning devices were provided if needed. Patients were asked to wear the stockings from getting up in the morning until retiring at night, for 2 years, and were encouraged to keep active. Three face-to-face follow-up visits were scheduled at 3 months (± 15 days), 1 year (± 1 month), and 2 years (± 1 month) from the baseline visit, in the afternoon to allow any PTS signs to become fully evident. Patients were instructed not to wear and not to bring their ECS on the day of the follow-up visit. In addition, patients were contacted by phone at 15 days (± 2 days), 6 months (± 15 days), and 18 months (± 15 days) to provide individual coaching on adherence, how to use ECS, and to check if they needed new ECS or needed to change the size. The data collected and examinations done (at each follow-up visit are summarised in the appendix p 9). The collection of ethnicity and race as a routine research variable is not authorised in France as per French data protection agency regulations (Commission Nationale Informatique et Liberté).

For the primary outcome, PTS was considered to be present if the Villalta score was 5 or higher in the leg ipsilateral to the initial DVT, at a single assessment, either at the 1 year or 2 year follow-up visits. Physical signs were assessed by investigators with the aid of a full-colour visual guide, and symptoms were rated by the patients. All investigators received individual training in PTS assessment before the beginning of the trial. If a patient could not attend the 2 year follow-up visit, a French version of the self-reported Villalta questionnaire, with instructions on how to fill it in, was sent to the patient.¹⁵ The Ginsberg method was used to assess the presence of PTS for the secondary outcome¹⁶ and the Villalta score was also used to assess the severity of PTS, which was considered as mild (with a score of 5–9), moderate (10–14), or severe (≥ 15 or if a venous ulcer was present).¹ Pain and oedema discomfort were assessed by weekly self-reporting from baseline to 3 months and by monthly self-reporting from 4 months to 24 months using the Visual Analogue Scale (VAS) to measure pain intensity. Signs of oedema were assessed by the investigator in addition to the previous outcome measure at 12 months and 24 months (pitting, ankle circumference).

Adherence was considered as optimal if the patient's self-reported use of the allocated study ECS was 80% or more of the time (based on the patient's diary or, if not filled in, according to adherence reported at each in-person or phone follow-up visit), and had a modified self-reported GIRERD adherence score (ie, a score that captures the patients' general attitude regarding their treatment) of 0–2.^{7,17} Adherence was defined as reasonable (corresponding to the expected adherence in routine clinical practice)¹³ if self-reported use of the

allocated study ECS was 50% or more of the study time and the modified self-reported GIRERD score was 0–2.

Safety was assessed during follow-up visits and phone contact or if patients contacted the investigator to report a problem. It was assessed by asking the patients whether they had any issues with wearing the stockings and if so what problems they had; at 3, 12, and 24 month follow-up visits we asked whether they had had venous thromboembolism recurrence, bleeding, or had had a cardiovascular event or cancer or any new health condition. Serious adverse events including death, major bleeding,¹⁸ and objectively confirmed venous thromboembolism recurrence as defined by the International Society on Thrombosis and Haemostasis¹⁹ were recorded. Death certificates or medical reports were collected from patient hospitalisations. Adverse events were classified as likely or unlikely to be due to study stockings.

The study expert committee, masked from treatment allocation, adjudicated all suspected venous thromboembolism events, death, major bleeding events, serious adverse events, and adverse events that could be related to ECS use as well as cases of PTS for which investigators felt there was a possible other explanation to a Villalta score of 5 or higher (ie, for the preplanned sensitivity analysis).

Quality of life was assessed at 3 months, 1 year, and 2 years using the generic EUROQOL EQ-5D questionnaire and the disease specific CIVIQ-20 questionnaire along with the compression stockings constraints questionnaire. The EUROQOL EQ-5D questionnaire has five questions on mobility, pain, self-care, usual activities, and psychological status with three possible answers for each item (ie, 1=no problem, 2=moderate problem, and 3=severe problem). A summary index with a maximum score of 1 can be derived from these five dimensions by conversion with a table of scores. The maximum score of 1 indicates the best health state. The CIVIQ-20 questionnaire has 20 questions focusing on four separate domain scores: physical, psychological impairment, social impairment, and amount of pain. All questions have a 5-point response category. The result is between 0 and 100, for which 0 is the best quality of life state.

Outcomes

The primary outcome was the cumulative proportion of PTS at 2 years and was measured using the clinical Villalta scale (≥ 5), as per the International Society on Thrombosis and Haemostasis guidelines.¹

Secondary outcomes were: (1) superiority testing of the primary outcome measure; (2) sensitivity analysis of the primary outcome after excluding patients with possible causes other than PTS to explain a Villalta score of 5 or more; (3) per protocol analysis among compliant (adherent) patients; (4) superiority of 25 mm Hg on the therapeutic compliance criterion at 2 years; (5) short-term changes in venous thrombosis symptoms (pain, oedema

discomfort) at 3 months; (6) long-term assessment of symptom changes and intensity related to the possible onset of PTS, including the presence of PTS and its severity, and pain and oedema discomfort; (7) quality of life, as assessed by patients using validated generic (EUROQUOL EQ5D-3L)²⁰ and venous-disease specific (CIVIQ-20)²¹ questionnaires; (8) Clinical-Etiology-Anatomy-Pathophysiology (CEAP) classification assessed by the investigator at 3 months, 12 months and 24 months; (9) assessment by Doppler ultrasound of the deep and superficial venous network at 3 months, 12 months and 24 months; thrombus burden will be assessed according to the LET US classification,²² which classifies DVT according to acute thrombus location and extent and reflux will be assessed in the common femoral, femoral veins at 1 year and 2 years, and considered as present if lasting longer than 1 s; (10) serious adverse events; (11) predictors of PTS; (12) subgroup analyses of primary and secondary outcomes by sex and age; and (13) examination of key factors for good compliance; psychological factors influencing adherence to ECS and patient's perceived constraints related to ECS use (appendix p 95). More detailed definitions of the outcomes can be found in the protocol (appendix pp 25–28). Results of all secondary analyses are presented in the Article.

Statistical analyses

We estimated that the cumulative proportion of PTS would be 25% in the 35 mm Hg ECS group.⁹ The CELEST Scientific Committee set the predefined non-inferiority margin for the difference in success rates at 12.5%. This difference was decided because of the absence of comparable available data; the non-life-threatening nature of the primary outcome, with most detected PTS expected to be mild;⁹ and that in a real-life setting the magnitude of the difference in adherence between 25 mm Hg and 35 mm Hg ECS is likely to be higher leading to an overall greater benefit of 25 mm Hg ECS in terms of PTS prevention (adherence to ECS is lower in real-life settings than in RCTs,¹³ as patients might be less motivated to wear ECS and do not usually have donning devices to put on ECS, which is more likely to affect adherence to 35 mm Hg ECS that are harder to put on than the 25 mm Hg ECS). Using a one-sided significance level of 0.05 and a power of 80%, we calculated that 296 patients would be needed. Assuming that the rate of loss-to-follow-up and death would be less than 15% (12.2% at 3 years in the open-label trial by Prandoni and colleagues),⁹ we planned to include 350 patients (ie, 175 per treatment group). The Data Safety Monitoring Board regularly reviewed study recruitment, patient retention, and safety outcomes.

Because we anticipated differences in adherence between groups (ie, better in the 25 mm Hg group than the 35 mm Hg group), we aimed to assess outcomes in a full analysis set comprised of all randomly allocated participants minus those individuals deemed ineligible

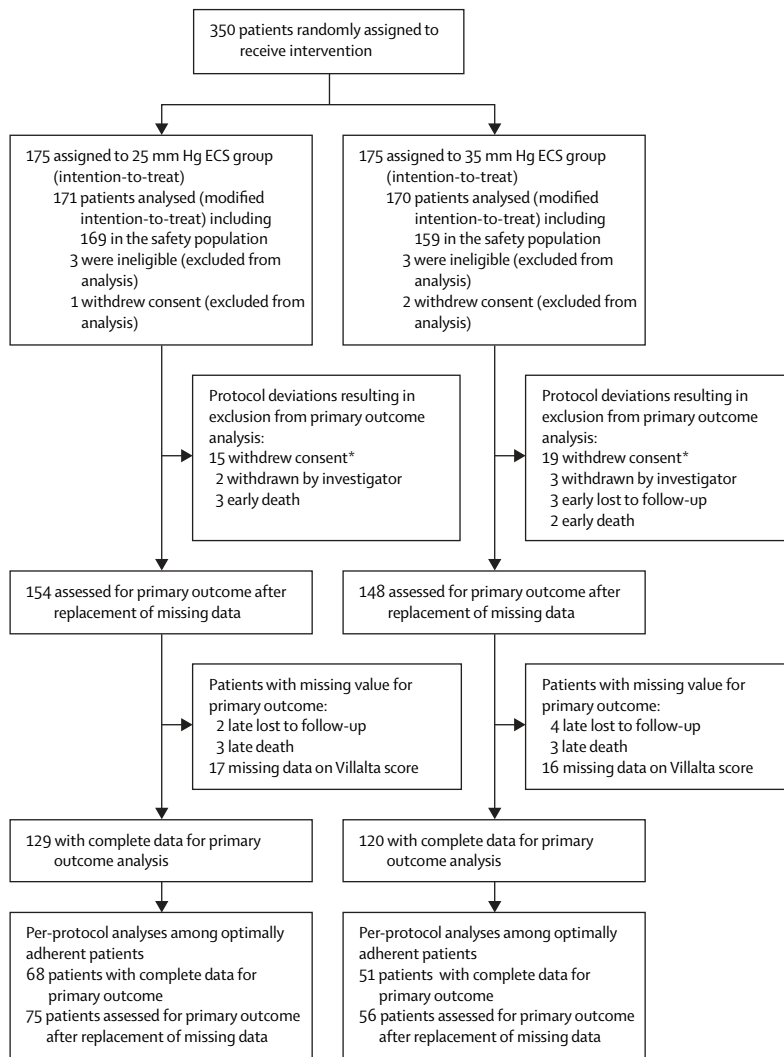


Figure 1: Trial profile

Of the ineligible patients in the 25 mm Hg group (n=3) two patients had bilateral proximal DVT and one had an ipsilateral trophic disorder. Of the ineligible patients in the 35 mm Hg group (n=3) one patient had bilateral proximal DVT, one had an ipsilateral isolated distal (and not proximal) DVT, and one had an ipsilateral trophic disorder. Of the patients withdrawn by investigators on behalf of the patient in the 25 mm Hg group (n=2) one patient had an allergic reaction to ECS and one was absolutely non-adherent to the study ECS. For patients withdrawn by investigators on behalf of the patient in the 35 mm Hg ECS group (n=3), one patient had inferior vena cava filter insertion for major bleeding and absolute contraindication to restart anticoagulation the day following randomisation, one was transitioned to palliative care, and one moved to a foreign country. DVT=deep vein thrombosis. ECS=elastic compression stockings. *Patients agreed that their data be used.

after randomisation or who withdrew consent and did not authorise us to use their data, with imputation for missing data. We decided to assess the primary and secondary efficacy outcomes in the complete case population (ie, without imputation because depending on the accuracy of imputation rules, the replacement of missing data can lead to unreliable results). However, we also present results with the imputed data, in which missing data on the primary outcome were replaced by a multivariable linear regression model including known and potential risk

factors for PTS (appendix p 3). We did not replace missing data in patients who withdrew consent (ie, for ethical and General Data Protection Regulation considerations). To test the hypothesis of superiority of 35 mm Hg versus 25 mm Hg for the prevention of PTS, per-protocol analyses were done among adherent patients without any major protocol deviation using the two different definitions of adherence: optimal ($\geq 80\%$ of the time) and reasonable ($\geq 50\%$ of the time). Adverse events were assessed among patients who had worn the study stockings at least once, and for whom we had at least some tolerance information during follow-up.

We calculated the 90% CI for the difference in the proportion of PTS between the 25 mm Hg and 35 mm Hg ECS groups. Non-inferiority was concluded if the upper limit of this CI was less than 12.5%. A two one-sided test with calculation of the p value associated with a one-tailed null hypothesis H_0 difference of 12.5% or higher was also done.²³ In addition, a Kaplan-Meier curve was used for representation of survival function (data censored at 760 days). If non-inferiority was achieved, superiority of the 25 mm Hg ECS compared with the 35 mm Hg ECS was to be tested. Comparison of overall rates of PTS between groups was done using the χ^2 test. Relative risks with 95% CIs were calculated. Preplanned subgroup analyses by age and sex and post-hoc analyses by BMI and the most proximal extent of index DVT were done by Mantel-Haenszel tests of homogeneity. Data on the comparison between below and above knee ECS are also provided; this analysis was not prespecified but added during peer review.

χ^2 or Fisher's exact tests as appropriate were used to assess qualitative secondary outcomes (ie, rates of patient adherence to ECS, the proportion of patients with PTS according to the Ginsberg method, with oedema, with reflux or with residual obstruction on ultrasound examination, patients' perceived constraints related to ECS, and psychological factors influencing adherence). Mann-Whitney tests were used for quantitative secondary outcomes (ie, Villalta score, pain, oedema, and leg volume), with presentation of median (25th and 75th percentiles) or median (10th and 90th percentiles). Mixed-design models for repeated measures with presentation of the p value associated with the time \times study treatment group interaction was used for quantitative secondary outcomes, to assess evolution over time (at months 3, 12, and 24) of results for the CIVIQ-20 and EUROQOL questionnaires in both groups. The Kruskal Wallis test was performed for general and venous disease-specific quality of life scores according to PTS severity. Independent predictors of PTS were assessed using a stepwise multivariable logistic model, which included variables (ie, baseline patients' and DVT characteristics, type of anticoagulant treatment, and adherence to ECS) that achieved a p value of 0.2 or less in univariate analysis as well as the ECS strength allocation group.

Cumulative rates of death, cancer, major bleeding, venous thromboembolism recurrence, and venous leg ulcer were estimated with the Kaplan-Meier method. Losses to follow-up, withdrawals, and deaths were censored as of the last date of follow-up.

Analyses were performed with STATA, version 15.0. The usual first-degree error of alpha less than 0.05 was used; one-sided for non-inferiority and two-sided for the other analyses.

This study is registered with ClinicalTrials.gov, NCT01578122.

Role of the funding source

Laboratoires Innothra approved the study protocol, manufactured the study ECS, suggested and funded an independent audit of all study data, funded English-language editing, and approved the final version of the manuscript. Laboratoires Innothra had no role in the collection, analysis, or interpretation of the data.

Results

350 patients were enrolled and randomised between June 28, 2012, and July 21, 2017 (figure 1, table 1). The last patient completed their 2 year follow-up on July 21, 2019. Nine (3%) of 350 participants were found to be ineligible after randomisation or withdrew consent, leaving 341 (97%) in the full analysis set. 233 (68%) of 341 patients were men, the median age was 59 years (IQR 45–70), and 17 (5%) of 337 patients with available data had previous ipsilateral distal DVT. 258 (76%) of 341 patients were randomised less than 3 days after DVT diagnosis and the most proximal extent of DVT was the iliac or femoral vein in 206 (63%) of 328 patients with available data (table 1).

During follow-up, 34 patients withdrew consent, five were withdrawn by the investigator, nine were lost to follow-up, and 11 died (figure 1). Baseline characteristics of patients who withdrew from the study did not differ between the 25 mm Hg and 35 mm Hg ECS groups. Median follow-up was 735 days (IQR 721–760); 734 days (IQR 719–760) in the 35 mm Hg group and 736 days (722–761) in the 25 mm Hg group. At 2 years, 294 patients were available for primary outcome analysis: 249 patients had complete data for primary outcome analysis and an additional 53 patients had some missing data that were replaced (figure 1). The characteristics of each group based on whether patients had some missing data on the primary outcome and whether data were replaced are presented in the appendix (p 2).

The cumulative proportion of PTS at 2 years was 40 (31%) of 129 patients in the 25 mm Hg ECS group versus 40 (33%) of 120 patients in the 35 mm Hg ECS group (figure 2). The absolute difference was –2.3% (90% CI –12.1 to 7.4; p=0.0062 for non-inferiority and –2.3%; 95% CI –13.9 to 9.3; p=0.70) for superiority. The relative risk was 0.93 (95% CI 0.65 to 1.33). Among patients randomised in the whole intention-to-treat population for whom we were authorised to use data, the

	25 mm Hg ECS group (n=171*)	35 mm Hg ECS group (n=170*)
Patients' characteristics†		
Median age, years	59 (47–69)	59 (44–71)
Sex		
Female	54 (32%)	54 (32%)
Male	117 (68%)	116 (68%)
Initial in-hospital management‡	129 (75%)	128 (75%)
BMI		
<25 kg/m ²	66 (39%)	58/169 (34%)
25–30 kg/m ²	69 (40%)	77/169 (46%)
≥30 kg/m ²	36 (21%)	34/169 (20%)
Previous venous thromboembolism	40 (23%)	30/166 (18%)
Cancer	20 (12%)	19/169 (11%)
Baseline contralateral Villalta score ≥5	14 (8%)	14/166 (8%)
DVT characteristics		
Unprovoked DVT	101/160 (63%)	92/152 (61%)
Time from DVT diagnosis to randomisation <3 days	124 (73%)	134 (79%)
Right leg DVT	70 (41%)	71 (42%)
Most proximal DVT extent		
Iliac	27/170 (16%)	27/158 (17%)
Femoral	82/170 (48%)	70/158 (44%)
Popliteal	61/170 (36%)	61/158 (39%)
Anticoagulant treatment		
Duration of treatment		
≤90 days	9/131 (7%)	9/126 (7%)
91–180 days	18/131 (14%)	19/126 (15%)
>180 days	104/131 (79%)	98/126 (78%)
Initial anticoagulant treatment low-molecular-weight heparin	119 (70%)	105/168 (63%)
Median duration of low-molecular-weight heparin, days	4 (2–19; n=103)	4 (2–8; n=88)
Long-term anticoagulant treatment		
Vitamin K antagonist	49/153 (32%)	45/152 (30%)
Direct oral anticoagulant	104/153 (68%)	107/152 (70%)

Table 1: Baseline characteristics

proportion of PTS was 45 (29%) of 154 patients in the 25 mm Hg group versus 52 (35%) of 148 patients in the 35 mm Hg ECS group (absolute difference –5.9%; 90% CI –14.7 to 2.9; p=0.0003 for non-inferiority) and relative risk=0.83; 0.60–1.16; p=0.27 for superiority.

In the per protocol analysis, cumulative proportion of PTS did not differ between groups irrespective of adherence (optimal or reasonable; table 2; appendix p 3). Results after replacing missing data and after excluding patients for whom another diagnosis was likely to explain a Villalta score of 5 or higher also did not differ

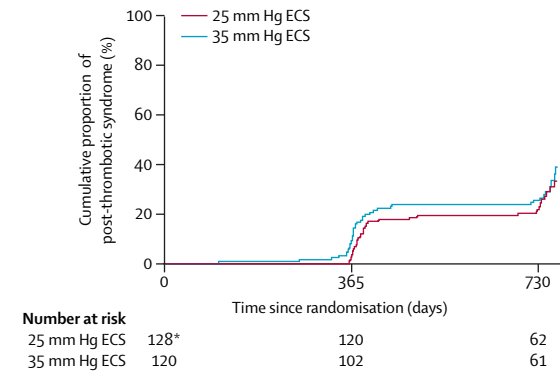


Figure 2: Cumulative proportions of post-thrombotic syndrome, in the 249 patients with complete datasets for the primary outcome
 ECS=elastic compression stockings. *On the day of the visit one patient had missing data.

between groups (appendix p 3). When focusing on adherence irrespective of allocated treatment group, the proportion of PTS seemed lower in patients who were at least reasonably adherent versus those who were not adherent. Adherence was optimal (>80% and modified GIRERD score of 0–2) for 75 (51%) of 146 patients assigned to 25 mm Hg ECS and for 56 (42%) of 134 patients assigned to 35 mm Hg ECS ($p=0.11$). 31 (26%) of 119 optimally adherent participants had PTS versus 44 (35%) of 124 non-optimally adherent patients ($p=0.11$). 41 (26%) of 159 reasonably adherent participants had PTS versus 34 (40%) of 84 non-reasonably adherent patients ($p=0.0018$). Evolution of adherence to study ECS over time, psychological factors influencing adherence, and perceived constraints associated with the use of ECS by treatment groups are presented in the appendix (pp 4–5).

When assessed using the Ginsberg method, the cumulative proportion of PTS did not differ in the 25 mm Hg ECS group (four [3%] of 126 patients) compared with the 35 mm Hg group (ten [8%] of 119 patients, $p=0.078$; table 2) and was lower when focusing on optimally adherent patients (three [5%] of 66 patients vs two [4%] of 50 patients; $p=0.99$).

Prespecified subgroup analyses by age, sex, BMI, and DVT location did not detect any significant differences between groups (appendix p 10). Moderate to severe PTS (ie, a Villalta score of ≥ 10 or the presence of a ipsilateral leg ulcer) developed in five (4%) of 129 patients in the 25 mm Hg ECS group and in 11 (9%) of 120 patients in the 35 mm Hg ECS group ($p=0.088$).

69 (36%) of 193 patients who initially chose to wear below the knee ECS developed PTS compared with 11 (20%) of 56 patients who initially chose to wear above the knee ECS ($p=0.023$). The proportion of optimally adherent patients was not statistically different among patients who originally chose to wear below the knee versus above the knee ECS: 88 (47%) of 188 patients versus 31 (56%) of 55 patients ($p=0.21$).

The main secondary efficacy outcomes, evolution of PTS scores over time, and predictors of PTS are presented in table 2 and the appendix (pp 3, 7–8).

Generic and disease specific quality of life scores did not differ between groups (appendix p 6). Between 3 months and 2 years, the generic EUROQUOL EQ5D-3L score increased from 0.89 (IQR 0.8–1.0) to 1.0 (0.8–1.0) in the 25 mm Hg ECS group and from 0.89 (0.8–1.0) to 0.91 (0.8–1.0) in the 35 mm Hg ECS group ($p=0.18$). The venous disease specific CIVIQ20 quality of life decreased from 11.3 (IQR 3.8–25.0) to 6.3 (1.3–15.6) in the 25 mm Hg ECS group and from 11.3 (5.0–25.6) to 8.8 (2.5–22.5) in the 35 mm Hg ECS group ($p=0.54$). Both generic and venous disease specific quality of life worsened with increasing PTS severity ($p<0.01$; appendix p 6).

Safety (ie, adverse events related or not to ECS use) was evaluated in 169 patients in the 25 mm Hg ECS group and 159 patients in the 35 mm Hg ECS group. Regarding adverse events, there were no between-group differences in rates of venous thromboembolism recurrence, ipsilateral DVT recurrence, major bleeding, or death between the 25 mm Hg ECS group and the 35 mm Hg ECS group (table 3). Two (1%) of 328 patients who ever wore ECS developed ECS-related serious adverse events, one distal DVT and one leg ulcer (both in the 35 mm Hg ECS group).

140 (83%) of 169 patients stated that they were unable to guess to which treatment group they had been assigned. In the 25 mm Hg ECS group, five (5%) of 93 patients provided a correct guess, 12 (13%) provided a wrong guess, and 76 (82%) were unable to guess their allocated treatment group. In the 35 mm Hg ECS group, eight (11%) of 76 patients provided a correct guess, four (5%) provided a wrong guess, and 64 (84%) were unable to guess their allocated treatment group.

Discussion

In the subset of patients with complete data for primary outcome analysis, 25 mm Hg ECS were non-inferior to 35 mm Hg ECS (absolute difference -2.3% ; 90% CI -12.1 to 7.4 ; $p_{\text{non-inferiority}}=0.0062$). The results remained unchanged after replacement of some missing data, after excluding patients for whom there was another explanation than PTS to explain a high Villalta score, which underline the robustness of our results.

Similarly, in our overall population (irrespective of allocated treatment group) the relative reduction in PTS between adherent and non-adherent patients was at least 33%, although this finding was only statistically significant in reasonably versus poorly adherent patients. This finding is consistent with a better efficacy of 35 mm Hg versus 25 mm Hg ECS when ECS are worn appropriately.

In terms of general and venous disease specific quality of life, our results show good quality of life scores in both groups at the end of follow-up, except among the few patients with moderate to severe PTS. Our results also

	25 mm Hg ECS group	35 mm Hg ECS group	p value
Primary outcome (for non-inferiority)			
Intention-to-treat			
Cumulative proportion of PTS, in patients with missing data replacement	45/154 (29.2% [22.2–37.1])	52/148 (35.1% [27.5–43.4])	0.0003
Cumulative proportion of PTS, in patients without missing data replacement	40/129 (31.0% [23.2–39.7])	40/120 (33.3% [25.0–42.5])	0.0062
Main secondary efficacy outcomes* (for superiority)			
Villalta severity category in patients without missing data replacement			
None (score <5)	89/129 (69.0% [60.3–76.8])	80/120 (66.7% [57.5–75.0])	..
Mild (5–9)	35/129 (27.1% [19.7–35.7])	29/120 (24.2% [16.8–32.8])	..
Moderate (10–14)	4/129 (3.1% [0.9–7.7])	6/120 (5.0% [1.9–10.6])	..
Severe (score ≥15 or ulcer)	1/129 (0.8% [0.02–4.2])	5/120 (4.2% [1.4–9.5])	..
Cumulative proportion of PTS in patients who are optimally adherent	20/68 (29.4% [19.0–41.7])	11/51 (21.6% [11.3–35.3])	0.34
Cumulative proportion of PTS when PTS assessed with Ginsberg's method	4/126 (3.2% [0.9–7.9])	10/119 (8.4% [4.1–14.9])	0.078
Median (10th–90th percentiles) Villalta score, continuous variable			
At 1 year	2 (0–6; n=139)	2 (0–7; n=134)	0.60
At 2 years	2 (0–6; n=129)	2 (0–7; n=119)	0.38
Median (25th–75th percentiles) pain ipsilateral vs contralateral leg			
At 1 week	8 (0–37; n=135)	16 (1–43; n=106)	0.13
At 3 months	1 (0–5; n=133)	0 (0–6; n=102)	0.35
At 1 year	0 (0–1; n=111)	0 (0–2; n=73)	0.48
At 2 years	0 (0–2; n=72)	0 (0–2; n=58)	0.24
Median (25th–75th percentiles) oedema ipsilateral vs contralateral leg, assessed by patient			
At 1 week	4 (0–40; n=133)	13 (0–47; n=106)	0.11
At 3 months	0 (0–4; n=134)	0 (0–7; n=102)	0.84
At 1 year	0 (0–1; n=109)	0 (0–4; n=73)	0.48
At 2 years	0 (0–1; n=71)	0 (0–1; n=58)	0.49
Ipsilateral leg oedema assessed by investigator			
At 1 year	27/135 (20.0% [13.6–27.7])	28/136 (20.6% [14.1–28.4])	0.90
At 2 years	24/131 (18.3% [12.1–26.0])	21/118 (17.8% [11.4–25.9])	0.92
Median (25th–75th percentiles) leg volume assessed in the leg ipsilateral to DVT, cm ³			
At 1 year	7459 (6285–8678; n=141)	7771 (6725–8948; n=136)	0.12
At 2 years	7579 (6318–8621; n=128)	7726 (6710–8771; n=120)	0.11
Ultrasonographic data at 3 months			
Residual venous obstruction in proximal deep veins	100/153 (65.4% [57.3–72.9])	95/146 (65.1% [56.7–72.8])	0.96
Deep venous reflux in leg ipsilateral to DVT	23/144 (16.0% [10.4–23.0])	22/139 (15.8% [10.2–23.0])	0.97
Ultrasonographic data at 1 year			
Residual venous obstruction in proximal deep veins	63/135 (46.7% [38.0–55.4])	63/133 (47.4% [38.7–56.2])	0.91
Deep venous reflux in leg ipsilateral to DVT	29/129 (22.5% [15.6–30.7])	34/131 (26.0% [18.7–34.3])	0.51
Ultrasonographic data at 2 years			
Residual venous obstruction in proximal deep veins	48/126 (38.1% [29.6–47.2])	43/119 (36.1% [27.5–45.4])	0.75
Deep venous reflux in leg ipsilateral to DVT	28/121 (23.1% [16.0–31.7])	21/115 (18.3% [11.7–26.5])	0.36

Data are n/N (% [90% CI]) for non-inferiority or (% [95% CI]) or median (IQR), unless otherwise stated. ECS=elastic compression stockings. PTS=post-thrombotic syndrome. DVT=deep vein thrombosis. *Other secondary outcomes (ie, proportion PST after excluding patients for whom another diagnosis than PTS was more likely to explain a Villalta score of ≥5, adherence and factors influencing adherence to ECS, constraints related to ECS, quality of life, and predictors of PTS) are presented in the appendix (pp 6–8).

Table 2: Main efficacy outcomes

confirm the good tolerance of ECS with very few reported significant side-effects.

Our study has limitations. First a greater-than-expected number of patients withdrew consent or were withdrawn from the study (11%). Even though this shortage was balanced between groups, the rate is higher than in the SOX (9%)¹¹ and the IDEAL-DVT (4%) studies.²⁴ This result might at least be in part the consequence of an adherence

coaching policy that was too strict. Furthermore, an additional 15% (n=53) of patients had missing data on the primary outcome. According to the statistical analysis plan these patients were not included in one of the two main primary outcome analysis done without variable imputation and we did not reach our expected sample size for the primary outcome analysis. In the absence of available published data we are not able to find out how

	25 mm Hg ECS group n=169	35 mm Hg ECS group n=159
Adverse events related to ECS		
Major adverse events related to ECS*	0 (0% [0-2.2])	2 (1.3% [0.2-4.5])
DVT	0 (0% [0-2.2])	1 (0.6% [0.02-3.5])
Infection	0 (0% [0-2.2])	0 (0% [0-2.3])
Ipsilateral leg ulcer	0 (0% [0-2.2])	1 (0.6% [0.02-3.5])
Death	0 (0% [0-2.2])	0 (0% [0-2.3])
Minor adverse events related to ECS (skin intolerance)	8 (4.7% [2.1-9.1])	6 (3.8% [1.4-8.0])
Adverse events (Kaplan-Meier Survival analyses)		
Ipsilateral leg ulcer	1 (0.7% [0.1-4.8])	3 (2.0% [0.7-6.2])
First recurrent venous thromboembolism (proximal DVT or PE)	14 (9.1% [5.5-14.9])	10 (7.0% [3.9-12.7])
Recurrent ipsilateral DVT (proximal or distal)	10 (6.5% [3.6-11.8])	11 (7.7% [4.3-13.4])
Major bleeding	7 (4.4% [2.1-9.0])	6 (4.1% [1.9-8.9])
Newly diagnosed cancer	6 (3.6% [1.6-7.8])	6 (4.2% [1.9-9.0])
Death	6 (3.9% [1.8-8.5])	5 (3.4% [1.4-8.0])
Cardiovascular event	4 (2.6% [1.0-6.7])	8 (5.5% [2.8-10.7])
Infection	6 (3.8% [1.7-8.3])	5 (3.4% [1.4-8.0])

Data are n (% or probabilities when Kaplan Meier analyses are done in the second part of the table [95% CI]).
ECS=elastic compression stockings. DVT=deep vein thrombosis. PE=pulmonary embolism. *One distal DVT and one leg ulcer.

Table 3: Safety and adverse outcomes in the modified intention-to-treat safety population

this rate of missing data on primary outcome compares with other similar ECS studies on PTS.^{11,24,25} However, this finding compares favourably to the large ATTRACT²⁶ RCT assessing the efficacy of pharmacomechanical catheter-directed thrombolysis to prevent PTS after a DVT in which 282 (41%) of 691 patients missed at least one PTS assessment. The baseline characteristics of patients with missing data, whether replaced or not, were similar to those of patients with complete data on the primary outcome and our results remained similar after replacement of missing data. We therefore believe that our study's main results are robust and valid. However, we have a lack of statistical power to show superiority of 25 mm Hg ECS in the overall population and of the 35 mm Hg ECS among optimally adherent patients. Importantly, the comparison of efficacy between 25 mm Hg ECS and 35 mm Hg ECS among adherent patients should be interpreted cautiously in light of the absence of a sample size estimation, formal randomisation (ie, secondary outcome analysis of a subpopulation), and probable differences in the patients' profiles between groups. Regarding generalisability, our study had many exclusion criteria. These criteria are justified by the fact that we wanted to exclude patients with pre-existing ipsilateral PTS or those who might have symptoms that could mimic PTS. Even though such selection is common in an RCT setting, we acknowledge that our population is not representative of the overall proximal DVT population. Furthermore, we do not have information on the proportion of patients in the CELEST trial that were inpatients at the time of randomisation, which constitutes

a potential source of selection bias. Our predefined non-inferiority margin (12.5%) is wider than in the OCTAVIA (10%)²⁴ and IDEAL-DVT (7.5%)²⁵ RCTs. Our non-inferiority criterion could be perceived as not being conservative enough. However, given our observed rates of PTS between groups, CELEST would still have concluded non-inferiority of 25 mm Hg ECS if our non-inferiority margin had been set at 7.5%. Similarly, in terms of PTS assessment, we assessed it on a yearly-basis, which is less frequent than in previous RCTs on ECS that usually assessed it every 6-months.^{8,9,11} This method might have contributed to a lower rate of PTS even though the rate of PTS we observed is consistent with what was reported in the 35 mm Hg group of ECS' RCTs and is lower than in the no-compression group of these RCTs (40–50%).^{8,9}

Regarding adherence to wearing ECS, our observed rate (56% of patients wore study ECS \geq 80% of the time) was lower than in most previously published RCTs (>75% of optimal adherence).^{8,9,24} In the absence of a standardised tool and protocol to report adherence, reliably comparing adherence between studies is difficult. However, in the CELEST study we paid particular attention to adherence (patients were phoned on a regular basis to remind them to wear their stockings) and to adherence reporting (use of a diary, considered as the gold standard for ECS adherence reporting).¹³ This attention might have led to a more precise assessment of lack of adherence. When using a more liberal definition of adherence, consistent with average adherence rates reported in routine practice (ie, use of ECS at least 50% of the time), more than 80% of CELEST patients could be considered as adherent. This number is in the range of the previously mentioned RCTs^{8,9,24} and higher than in the SOX study (56% of patients wore ECS >3 days per week).¹¹ Finally, despite a low production cost, the expected direct economic benefit for the patient depends on their health system's pricing policies. Indeed, 25 mm Hg ECS are cheaper to buy than 35 mm Hg ECS in some but not all countries.

Among the strengths of our study was that it was double-blinded, which remains challenging in the field of compression therapy. To the best of our knowledge, CELEST is the first study comparing two different strengths of ECS to prevent PTS after an acute proximal DVT. The study does not formally address the question of ECS efficacy but rather attempts to determine the optimal strength of ECS to prevent PTS. We cannot exclude that the absence of difference between groups, despite a seemingly dose-relationship effect, is not the consequence of an absence of efficacy of ECS in preventing PTS. A large choice of stockings was offered to patients and donning devices were provided. The baseline characteristics of our study population were well balanced between groups; around 75% of patients were randomised less than 3 days after DVT diagnosis and compression therapy was started just after randomisation

with the use of 20–36 mm Hg ECS. This method did not affect patients' blinding, as, at the end of the study, the vast majority of patients in each group were unable to guess or wrongly guessed their allocated treatment group. Finally, all patients were followed up and assessed for signs of PTS by vascular medicine physicians specialised in the management of DVT and chronic venous disorders.

What are the practical clinical implications of the CELEST findings? CELEST provides indirect additional data suggesting that, as shown in some previous open-label studies,^{8,9,25,27} the use of ECS influences the development of PTS. Therefore, to consider offering ECS to patients with acute symptomatic proximal DVT in a PTS prevention strategy, which validates and confirms a common therapeutic attitude, seems reasonable.⁶ However, as underlined in previous RCT and routine clinical practice studies,^{10,11} achieving optimal adherence is difficult in the long-term and this reality likely affects the efficacy of ECS-based PTS prevention approaches. We also found that use of lower-strength (ie, 25 mm Hg) ECS seems to improve adherence to ECS and seems at least as effective as tighter ECS in preventing PTS. As lower strength ECS are easier to put on and as below-knee ECS are better tolerated, leading to less treatment discontinuation, and as effective as above knee ECS,²⁸ the use of 25 mm Hg below-knee ECS could be favoured. The possible greater efficacy of higher strength ECS (ie, 35 mm Hg than 25 mm Hg ECS) in optimally adherent patients suggests that patients at high-risk of PTS, such as those with iliac DVT, who are motivated and expected to be adherent to wearing stockings might be offered 35 mm Hg rather than 25 mm Hg ECS. Moreover, and to complete this update on ECS-based PTS prevention strategies, based on previous studies published after the CELEST study was started, the duration of ECS therapy should be decided on an individual patient basis and ECS treatment can be safely stopped after 6 months in most,²⁴ but not all²⁵ patients.

In conclusion, although we did not reach the pre-specified sample size, our results suggest that 25 mm Hg ECS are non-inferior to 35 mm Hg ECS in preventing PTS. As they are easier to put on and similarly safe, the use of 25 mm Hg ECS could be favoured over higher strength ECS in the overall proximal DVT population, to prevent PTS. High strength ECS might be preferable in patients at high risk of PTS and who are expected to be optimally adherent to wearing ECS. This conclusion needs to be confirmed by larger and better powered studies than the CELEST trial. Further studies are also needed to better identify the role and the strength of ECS for PTS prevention on an individual patient basis. The ongoing CHAPS study (NCT04103112)²⁹ should provide important additional information on the effect of low strength ECS (ie, 23–32 mm Hg) versus no ECS on the risk of PTS.

CELEST trial investigators

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Contributors

J-PG contributed to the conceptualisation, investigation, and writing of the original draft. CG-V contributed to the formal analysis, visualisation, writing, reviewing, and editing. M-TB, FB, and M-AS contributed to the conceptualisation, writing, reviewing, and editing. VJ and FV contributed to the conceptualisation and manuscript approval. SB, AB-R, PO, CRI, and JS contributed to the conceptualisation, investigation, writing, reviewing, and editing. AC contributed to the project administration, investigation, writing, reviewing, and editing; CG, HG, and MM contributed to the investigation, writing, reviewing, and editing. CRo contributed to the project administration, investigation, supervision, writing, reviewing, and editing. J-LB contributed to the conceptualisation, method, supervision, funding acquisition, formal analysis, visualisation, writing, reviewing, and editing. J-PG, CG-V, and J-LB had access to the raw data and had final responsibility for the decision to submit for publication.

Declaration of interests

All authors declare financial support from Laboratoires Innothera for the submitted work through their institutions. VJ and FV are employees of Laboratoires Innothera but were not involved in the analysis and interpretation of data, or in writing the Article. AB-R declares consultant fees and travel grants from Bristol-Myers Squibb Pfizer and Bayer. SB declares honoraria from Urgo and Thuasne.

Data sharing

The authors commit to making the relevant deidentified participant data (with a data dictionary) available to others on reasonable request to the corresponding author, after publication, and with a signed data access agreement. The full study protocol is available online at the Grenoble University Hospital clinical investigation centre website.

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