

REVIEW ARTICLE

Compression stockings to prevent postthrombotic syndrome: Literature overview and presentation of the CELEST trial

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Abstract

Postthrombotic syndrome (PTS) is a burdensome and costly complication of deep vein thrombosis (DVT) that develops in 20%-40% of patients within 2 years after proximal DVT. In the absence of effective curative treatment, management of PTS relies on its prevention after DVT. The effectiveness of elastic compression stockings (ECS) to prevent PTS is uncertain. We present an overview of published studies assessing the efficacy of ECS to prevent PTS and present the protocol for the CELEST clinical trial. While previous open-label randomized trials have reported a 50% risk reduction in PTS in patients treated with >30 mm Hg ankle pressure ECS, a large double-blind trial reported no effect of ECS. We discuss the main potential limitations of these trials, including a placebo effect and suboptimal compliance to ECS. We present the protocol of the CELEST double-blind randomized trial comparing 2 years of high strength (ankle pressure 35 mm Hg) versus lower strength (ankle pressure 25 mm Hg) ECS in the prevention of PTS after a first acute symptomatic, unilateral, proximal DVT. The use of lower-strength ECS than that used in previous studies should favor compliance. CELEST may provide important evidence about the efficacy of ECS in the prevention of PTS after DVT. The results will be interpreted in the light of results from recent clinical trials assessing ECS for PTS prevention that reported that the duration of ECS use should be tailored to the individual, if ECS are efficacious in the prevention of PTS.

KEYWORDS

clinical trial, compression stockings, deep vein thrombosis, postthrombotic syndrome, venous thrombosis

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Essentials

- Efficacy of elastic compression stockings (ECS) in the prevention of postthrombotic syndrome (PTS) after deep vein thrombosis (DVT) is uncertain.
- Discrepancy between randomized controlled trials (RCTs) may be explained by the placebo effect and/or suboptimal compliance.
- Lower-strength ECS should improve compliance, but their efficacy has not been established.
- The CELEST double-blind RCT will compare high- versus lower-strength ECS to prevent PTS after a first DVT.

1 | INTRODUCTION

Postthrombotic syndrome (PTS) refers to chronic venous insufficiency (CVI) manifestations following deep vein thrombosis (DVT).¹ It is an important long-term adverse outcome of venous thromboembolism (VTE), in addition to VTE recurrence and chronic thromboembolic pulmonary hypertension.² PTS develops in 20%-40% of patients after proximal DVT.³ Although it is not lethal, it can have serious medical, social, and economic consequences.⁴

In the absence of effective treatment for established PTS, management of PTS is challenging and is mainly focused on prevention.^{5,6} Before 2014, the mainstay of prevention included the use of elastic compression stockings (ECS) for 2 years, with optimal anticoagulant treatment to prevent DVT.⁷⁻¹⁰ This was mainly based on the results of two small open-label randomized controlled trials (RCTs) that showed a significant 50% risk reduction in PTS in patients treated with >30 mm Hg ankle pressure ECS versus no ECS after an acute proximal DVT.^{11,12} The results of a large randomized RCT, the SOX (Compression Stockings to Prevent the Post-Thrombotic Syndrome) trial, did not provide evidence of efficacy of this simple, harmless treatment versus placebo ECS.¹³ There are several potential explanations as to why rigorously conducted trials report opposite results, and ECS efficacy is now debated.¹⁴ This lack of agreement on the efficacy of ECS among experts led to several guidelines no longer recommending ECS for the prevention of PTS, leaving physicians “empty handed.”^{6,15-21} In this article, we present an overview of the published clinical trials that have assessed the efficacy of ECS in the prevention of PTS after an acute DVT and examine their limitations. We will then present the protocol of the CELEST trial (Compression Elastique Evaluation du Syndrome post Thrombotique), a multicenter double-blind RCT comparing high-strength (ankle pressure 35 mm Hg) versus lower-strength (ankle pressure 25 mm Hg) ECS to prevent PTS after proximal DVT.

2 | OVERVIEW OF PUBLISHED CLINICAL TRIALS ON ECS TO PREVENT PTS

We (JPG and JLB) made a PubMed and clinical trials.gov search on May 25, 2020, using the terms *postthrombotic syndrome*, *postphlebotic syndrome*, and *compression* to identify RCTs and meta-analyses

published after SOX publication in 2014 that have assessed the efficacy of ECS (vs placebo or no ECS) to prevent PTS after an *acute* DVT. We identified four RCTs.^{11-13,22} Their design and main results are presented in Table 1. Two studies reported that ECS were effective^{11,12} and two did not.^{13,22} Eight meta-analyses have been published since the publication of SOX study in 2014.²³⁻³⁰ Three of these meta-analyses concluded that ECS might/could be efficacious with an approximate 30% risk reduction of PTS,^{23,24,29} three concluded that ECS might/could not be efficacious,^{27,28,30} and the remaining ones reported no conclusion because they felt that the trials were too heterogeneous and sampling bias was too high.^{25,26} All meta-analyses agreed on the need for additional studies. This underlines the high level of uncertainty surrounding the question of ECS efficacy and raises a first question: Why would ECS be effective in preventing PTS?

3 | PATHOPHYSIOLOGICAL RATIONALE SUPPORTING THE USE OF ECS FOR PTS PREVENTION

ECS have been shown indisputably to prevent edema, heal and prevent venous ulcers, and provide symptom relief in individuals with venous and lymphatic disorders.³¹ The mechanism of action of ECS is straightforward: stockings oppose gravitational forces and decrease ambulatory venous pressure, thereby reducing the volume in veins and tissues.³² This then reduces edema, restores microcirculation, and improves calf muscle pump efficiency.⁵

The pathophysiological rationale supporting the efficacy of ECS to prevent PTS is less clear-cut. Several studies have shown that patients with DVT or superficial venous thrombosis who wore ECS had better or faster recanalization rates than those who did not.^{14,33-35} Furthermore, ECS were found to reduce markers of inflammation in patients with venous ulcers,³⁶ and in mouse models, stasis is associated with increased inflammation and impaired thrombus resolution.³⁷ By reducing inflammation, prompting thrombus resolution, ECS may prevent vein wall fibrosis and preserve venous valves. Thus, theoretically, ECS could target the three main pathophysiological mechanisms of PTS: inflammation, venous obstruction, and venous reflux. However, it is important to remember the potential presence of important limitations (see below) in each of the published RCTs when considering the debate about the efficacy of ECS.

TABLE 1 Characteristics of RCTs comparing ECS versus no ECS or placebo ECS to prevent PTS after acute DVT

	Brandjes, 1997 ¹¹	Prandoni, 2004 ¹²	Kahn, 2014 ¹³	Javaraj, 2015 ²²
Number of participants	194	180	803	69
Design	Open label	Open label	Placebo controlled	Open label
Country, centers	Netherlands, 2 centers	Italy, 1 center	Canada, United States, 24 centers	United States, 2 centers
Trial arms	40 mm Hg ECS No ECS	30-40 mm Hg ECS No ECS	30-40 mm Hg ECS Placebo ECS (<5 mm Hg)	30-40 mm Hg No ECS
Inclusion criteria	Venogram-proven first unilateral proximal DVT	US-proven first ipsilateral unilateral symptomatic proximal DVT	US-proven first symptomatic proximal DVT < 14 d	US-proven first proximal DVT
Main exclusion criteria - CVI - Use of ECS at randomization	Leg ulcer, extensive varicosities excluded Exclusion criterion	Leg ulcer, signs of CVI excluded -	NA NA	CEAP 4-6 excluded Exclusion criterion
PTS assessment	Modified Villalta scale on 2 consecutive assessments \geq 3 mo apart, \geq 6 mo after DVT dg	Villalta scale: VS \geq 5 on 2 consecutive assessments starting 3 mo after DVT dg	Ginsberg method Villalta scale (VS \geq 5 once) starting \geq 6 mo after DVT dg	Villalta scale VCSS
ECS type	Made-to-measure knee-length	Ready-made knee-length	Ready-made knee-length	Ready-made knee-length
Time between DVT dg and ECS use	2-3 wk	1 wk (at hospital discharge)	1 wk, (2 wk max)	48 h
ECS supply	2 ECS, replaced/6 mo	2 ECS, replaced/6 mo	2 ECS, replaced/6 mo	3 pairs ECS/4 mo
Assessment compliance	Self-reported, interview at each FU visit	Self-reported (notebook), at each FU visit	Self-reported, at each FU visit	Self-reported, interviews at least every month
Duration ECS use	At least 2 y	2 y	2 y	2 y
FU visit	Every 3 mo for 2 y, then every 6 mo for up to 5 y	At 3 mo, then every 6 mo	At 1 month, then every 6 mo	At 1 and 3 mo, then every 6 mo
Median follow-up	76 mo	49 mo (at least 3 y)	24 mo	12 mo
Mean age	60	62	55 y	48 y
Males	56%	43%	60%	51%
AC treatment	At least 3 mo No FU data	At least 3 mo Median, 6 mo both groups	... Median, 6 mo in both groups	Must receive some AC No FU data
Death	18% (n = 35, 19 and 16)	10.6% (n = 19, 7 and 12)	9.0% (72, 36, and 36)	Not reported
Loss to FU	3.6% (n = 7, 4, and 2)	1.7% (n = 3, 1, and 2)	5.5% (n = 44, 23, and 21)	54% (n = 37, 19, and 13), including death
Withdraw from study	Included in loss to FU	6.7% (n = 6, ECS group)	8.7% (n = 70, 33, and 37)	
PTS (ECS vs placebo/no ECS)	6-y cum inc: 31.3% (n = 40) vs 70.4% (n = 69), P < .001	At most 5-y cum inc: 25.7% (n = 23) vs 49.1% (n = 44), P < .01	2-y cum inc: G:14.2% (n = 44) vs 12.7% (n = 37), NS	2-y cum inc: No numeric data provided.
Overall	11.5% (n = 11) vs. 23.5% (n = 23), P < .001	3.5% (n = 3) vs 11.7% (n = 1), P = .01	VS: 52.6% (n = 176) vs. 52.3% (n = 168), NS	NS difference if PTS assessed \geq 6-mo DVT Dg
Severe PTS			VS: 7.5% (n = 27) vs 5.8% (n = 20), NS	
QOL	Not assessed	Not assessed	SF-36, VEINES-QOL No difference between groups	Not assessed
Reported compliance with ECS at 2 y	93% >80% of time 76% always	87% >80% of time 93% if FU achieved	56% >3 d a wk	60%
VTE recurrence	14.6% (n = 14) vs 13.3% (n = 13), NS	13.3% (n = 12) vs 14.4% (n = 13), NS	8.1% (n = 33) vs 9.6% (n = 38), NS	No data

(Continues)

TABLE 1 (Continued)

	Brandjes, 1997 ¹¹	Prandoni, 2004 ¹²	Kahn, 2014 ¹³	Javaraj, 2015 ²²
Side effects of ECS	No data	Itching, redness, discomfort: 6% (n = 5) ECS group	Itching rash: 2% each group	No data

Abbreviations: AC, anticoagulant; cum inc, cumulative incidence; CVI, chronic venous insufficiency; dg, diagnosis; DVT: deep vein thrombosis; ECS: elastic compression stockings; FU: follow-up; NA, not applicable; NS, not statistically significant difference; PTS, postthrombotic syndrome; US, ultrasound; VCSS, Venous Clinical Severity Score; VEINES-QOL, Venous Insufficiency Epidemiological and Economic Study–Quality of Life; VS, Villalta score; VTE, venous thromboembolism.

4 | POTENTIAL LIMITATIONS OF PUBLISHED RCTS ASSESSING THE EFFICACY OF ECS IN THE PREVENTION OF PTS AFTER ACUTE DVT

Three important limitations that could explain why some RCTs failed to demonstrate the efficacy of ECS or why others may have erroneously reported efficacy have been identified.

4.1 | Placebo effect

The placebo effect can be defined as improvement or change in subjective discomfort or illness resulting from an intervention with no physical effect.³⁸ The mechanisms of the placebo effect are not well understood but are thought to be related to the power of the brain to affect bodily sensations and functions. This effect is particularly likely to occur in diseases with subjective symptoms such as PTS, although it has also been reported in severe diseases with objective measurements, such as angina pectoris.^{38,39} The interaction between the caregiver and the patient can strongly enhance the placebo effect.⁴⁰ A potential placebo effect has been suggested to explain the 50% risk reduction in PTS in the ECS groups in open-label RCTs.^{11,12,25} One study reported higher efficacy of ECS on symptoms rather than on objective signs of PTS.¹² However, two RCTs reported that the beneficial effect of ECS was present in subgroups of patients with severe PTS, where a placebo effect is less likely.^{11,12} Only a well-designed double-blind RCT that minimizes this bias could provide definitive evidence of the efficacy or inefficacy of ECS.

4.2 | Suboptimal compliance

It has been suggested that the negative results in the SOX trial can be explained by a lower rate of compliance to ECS use than in other trials. In the SOX trial only 55.6% of patients reported using stockings >3 days per week at the end of follow-up compared with 76% of patients who reported wearing ECS all the time and 86.6% of patients reported wearing ECS >80% of time in the open-label trials.¹¹⁻¹³ However, as 52% of patients developed PTS, as assessed by the Villalta score in the SOX trial, a substantial underlying effect

should have been detected, if the 50% hazard reduction reported for compliant patients in the open-label studies were present, despite the low compliance.²⁸ Furthermore, the SOX trial reported that frequent ECS use did not improve the results.

In line with previous studies, the main reason for noncompliance reported by the patients in the SOX trial was difficulty putting the stockings on.⁴¹⁻⁴³ Similarly, in the IDEAL-DVT (Individually Tailored Elastic Compression Therapy After Deep Venous Thrombosis in Relation to the Incidence of Post Thrombotic Syndrome) trial, the second most important determinant of good compliance, after PTS risk reduction, was the ability to put the ECS on independently.⁴⁴ Unquestionably, compliance is the Achilles heel of ECS therapy, and in routine clinical practice, compliance with ECS appears to be similar to that reported in the SOX trial⁴⁵⁻⁴⁷ rather than that reported in the positive open-label trials.^{11,12}

One reason that could explain the differences in compliance rates between the SOX trial and the open-label trials could be that, in routine clinical practice in Canada, where the trial was performed, physicians rarely prescribe ECS after DVT.^{48,49} This is in contrast to practice in most European countries (including those where the positive open-label trials were conducted) and endorsement of ECS use by physicians has been shown to increase ECS compliance compared with providing minimal explanation to patients.^{44,48,50} Another reason could be that differences in investigators' and patients' reporting practices may have accounted for some of the differences. A recent literature review showed that compliance reporting is usually poor in studies, particularly when there is no standardized tools collecting data.⁵¹ Future RCTs assessing the efficacy of ECS should encourage compliance with ECS, via promoting physicians' endorsement of ECS use, scheduling regular phone contact with the patient to reinforce compliance and improve reporting by the use of prospectively maintained diaries, which are the current "gold standard" for ECS compliance assessment.⁵¹ However, beyond these measures, use of lighter ECS is probably one of the best and easiest ways to improve ECS compliance.⁵²

4.3 | Timing of ECS use

In the SOX trial protocol, ECS should have been used within 2 weeks of the DVT diagnosis. It has been suggested that the

absence of compression at the very acute phase of DVT may have played a role in final outcome.^{28,53} Lower rates of PTS have been reported in some studies when compression is used earlier.^{14,33,34,54} However, from a practical point of view, ECS were not applied earlier in the open-label trials that reported positive results for ECS (2 weeks and 1 week, respectively) compared with in the SOX trial (1 week on average). Without questioning the potential benefits of applying compression early, this is unlikely to explain the differences between the results from open-label trials and the SOX trial.⁵⁵

4.4 | Other potential limitations

The other following limitations have been reported:

- A possible therapeutic effect of placebo stockings in SOX
- Differences in the characteristics of patients' and of their DVTs between trials
- Differences in anticoagulant treatments between trials

Thus, it is unclear if the use of ECS prevents PTS in patients after acute DVT. Well-designed, randomized, double-blind trials, with good compliance to ECS, are needed to provide definitive evidence of efficacy, or lack of efficacy of ECS.^{29,30,56,57} Use of lighter strength of compression than previously used (>30 mm Hg), cautious patient education, and regular monitoring of ECS compliance should favor compliance in the long-term.

5 | THE CELEST TRIAL

The CELEST trial is a French, multicenter, double-blind, RCT assessing the efficacy of 2 years of high-strength (ankle pressure 35 mm Hg) versus lower-strength (ankle pressure 25 mm Hg) ECS to prevent PTS after a first proximal DVT. When the protocol was finalized in 2012, the SOX trial had not been published¹³ and at that time the use of 30-40 mm Hg ECS was considered as a simple and effective measure to prevent PTS.^{7,9,10} However, in routine clinical practice, lighter strengths of ECS were often prescribed.^{48,49,58,59} In a survey conducted in France in 2009 among 761 vascular medicine physicians, 96% stated that they systematically prescribed ECS after DVT.⁵⁸ In contrast with guidelines, two-thirds stated that they prescribed lighter ECS than the recommended ones (30-40 mm Hg), mainly to favor compliance.¹⁰ At pressures as low as 20-30 mm Hg, ECS have been shown to improve calf muscle efficiency and to relieve symptoms, reduce edema, and prevent and heal trophic disorders.^{32,60,61} Nevertheless, it was unknown if this lower pressure could also be efficacious in PTS prevention.

To confirm the safety of this routine clinical practice, TIMC (University Grenoble Alpes AND CNRS) and Laboratoires Innothra (sponsor) decided to conduct a clinical trial comparing the efficacy of high-strength (ankle pressure 35 mm Hg) versus lower-strength

(ankle pressure 25 mm Hg) ECS in the prevention of PTS. The trial was endorsed by the French Society of Vascular Medicine. The CELEST trial started enrolling patients in June 2012. Patients were recruited over 61 months, and follow-up ended in June 2019. Final audit of data is expected was completed in October 2020, and statistical analysis is expected to be started in November 2020.

5.1 | Objectives of the study

The primary objective of the study is to assess if 25 mm Hg ECS are noninferior to 35 mm Hg ECS for the prevention of PTS in patients after a first proximal DVT. We expect that the potential lower efficacy of 25 mm Hg ECS in compliant patients will be balanced by a lower compliance rate to 35 mm Hg ECS, leading to an overall similar efficacy.

The secondary objectives were to assess:

1. If 25 mm Hg ECS are superior to 35 mm Hg for the prevention of PTS. This could be achieved if the efficacy of 25 mm Hg ECS are similar to that of 35 mm Hg ECS and if compliance is higher for the 25 mm Hg ECS.
2. If 25 mm Hg ECS are noninferior to 35 mm Hg ECS to prevent PTS in patients with proximal DVT after excluding patients who have a differential diagnosis that could explain a Villalta score ≥ 5 (sensitivity analysis). Indeed, signs and symptoms of PTS/CVI are nonspecific and unlikely to be improved by ECS.⁶²
3. If 35 mm Hg ECS are superior to 25 mm Hg ECS to prevent PTS in the subgroup of patients compliant with ECS. If ECS are efficacious in the prevention of PTS, a dose-response relationship may exist, and higher pressure applied could be expected to result in a greater therapeutic effect.³²
4. If the compliance to 25 mm Hg ECS is superior to that for 35 mm Hg ECS at 2 years of follow-up.
5. If the quality of life (QOL) is superior and ECS constraints are inferior in the 25 mm Hg ECS group to those in the 35 mm Hg ECS group. As 25 mm Hg ECS are easier to put on, this should reduce wearing constraints and improve venous QOL.
6. If 25 mm Hg ECS and 35 mm Hg ECS have similar efficacy in reducing the patient's self-reported pain and edema discomfort up to 3 months after DVT.
7. If the evolution of general QOL scores are similar in the 25 mm Hg ECS and 35 mm Hg ECS groups.
8. If 25 mm Hg ECS and 35 mm Hg ECS have similar efficacy in the prevention of patient's self-reported pain and edema discomfort at 12 and 24 months.
9. If 25 mm Hg ECS and 35 mm Hg ECS have similar efficacy in the prevention of venous trophic disorders (Clinical Etiological Anatomical Pathophysiological classification [CEAP], C4-C6).
10. If 25 mm Hg ECS and 35 mm Hg ECS have similar efficacy in the prevention of ultrasonographic postthrombotic sequelae at 3-month, 1-year, and 2-year follow-up.
11. To assess predictors of PTS.
12. To assess predictors of compliance to ECS use.

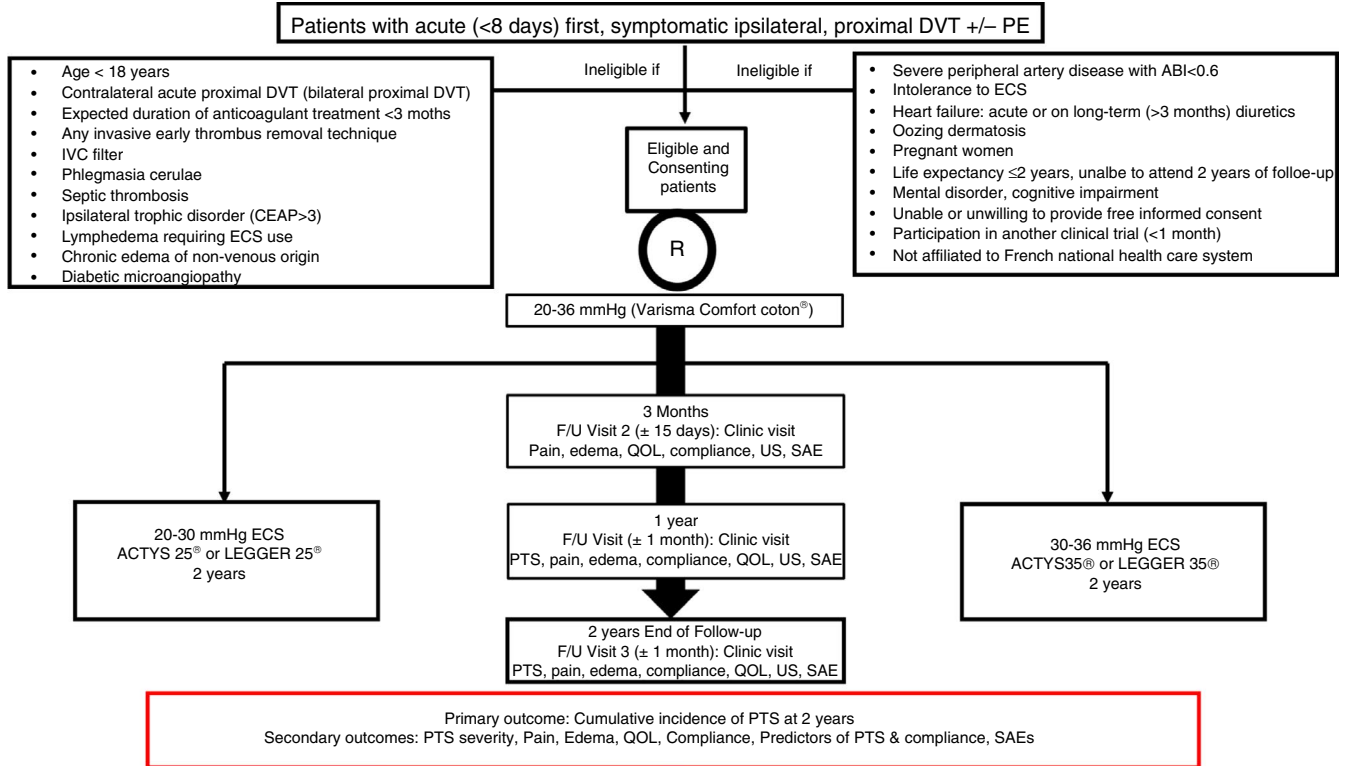


FIGURE 1 CELEST study flow diagram. ABI, ankle brachial index; CEAP, Clinical Etiological Anatomical Pathophysiological classification; DVT, deep vein thrombosis; ECS, elastic compression stockings; F/U, follow-up; IVC, inferior vena cava; PE, pulmonary embolism; PTS, postthrombotic syndrome; QOL, quality of life; SAE, serious adverse event; US, ultrasound

13. To describe rates of VTE recurrence, any-cause death, fatal pulmonary embolism, venous ulcers, and any possible side effect of study treatment (eg, peripheral arterial disease decompensation, rashes).
14. To perform subgroup analyses of primary and secondary objectives according to sex and age, and analysis of primary objective, using the Ginsberg criteria for the diagnosis of PTS.⁶³

5.2 | Description of the study procedures

This study is being conducted in 46 French private practice offices and hospital-based vascular medicine wards. The clinical trial coordinating center is located in Grenoble (TIMC-IMAG), and the principal investigator is Dr Jean-Luc Bosson. The study inclusion and exclusion criteria are summarized in Figure 1. Briefly, adult patients with a first, acute, symptomatic, objectively confirmed, ipsilateral proximal DVT (calf trifurcation or above) were eligible.

At baseline inclusion visit, patients' demographics, past medical history, risk factors for VTE, usual medications, and current DVT management were collected. Patients had a full clinical examination, including bilateral CEAP, Villalta score, edema, ankle brachial indexes, Godet's sign, and ankle perimeter assessments and measurements for ECS sizing (on DVT-affected leg). A bilateral whole leg ultrasound (US) was also done. Patients were instructed on how

to put on the ECS and were given a diary to record compliance, symptoms, and any adverse events or treatment modifications. This diary also contained educational materials and was replaced at 3 months, 6 months, and then every 6 months. Patients were asked to wear ECS from when they woke up until they went to bed for 2 years.

Patients were randomized online using Clininfo software (Lyon, France) (random block size, stratified by center, age, and sex) to receive either 25 mm Hg custom-fitted ECS (ACTYS 25 (Innothera, Arcueil, France) in women, LEGGER 25 (Innothera, Arcueil, France) classic in men) or 35 mm Hg custom-fitted ECS (ACTYS 35 in women, LEGGER 35 in men). Two pairs of trial custom-fitted ECS were sent to the patient by mail via the trial coordinating center within 10 days of randomization. ECS were changed every 3 months and more frequently if required. Patient could choose between knee-length or thigh-length ECS, based on the CANANO trial results that showed similar efficacy for both, as well as the color and open- or closed-toe models.⁶⁴ Donning devices were provided if needed. At the baseline visit, patients were given commercialized ECS stockings (VARISMA Comfort Coton model (innothera, Arcueil, France), 20-36 mm Hg [different type and strength from trial ECS]) to be worn until they had received the trial ECS.

Three face-to-face follow-up visits were scheduled at 3 months (±15 days), 1 year (±1 month), and 2 years (±1 month), in the afternoon. Patients were instructed not to wear and not to bring their ECS on the day of the follow-up visit. In addition, patients were

TABLE 2 CELEST: procedures undertaken at in-person and phone follow-up visits

Visit →	1	2	3 ^a	4	5 ^a	6	7*
Timing →	Enrollment	15 d ± 2 d	3 mo ± 15 d	6 mo ± 15 d	1 y ± 1 mo	18 mo ± 15 d	2 y ± 1 mo
Type of visit	In person	Phone call	In person	Phone call	In person	Phone call	In person
Baseline CRF	X						
F/U form			X		X		X
Concomitant medications	X		X		X		X
Pain VAS	X	X	X	X	X	X	X
Edema discomfort VAS	X	X	X	X	X	X	X
Villalta PTS scale	X				X		X
Ginsberg scale					X		X
CEAP classification	X		X		X		X
ABI	X		X		X		X
QOL questionnaires (EQ5D3L, CIVIQ)			X		X		X
Compliance check		X	X	X	X	X	X
Ultrasound	X		X		X		X
SAE form	To be completed whenever an SAE is suspected						
Suspected VTE event form	To be completed whenever a recurrent VTE event is suspected						
Major and clinically relevant nonmajor bleeding event form	To be completed whenever a major or a clinically relevant nonmajor bleeding is suspected						
Termination form	To be completed whenever a patient is terminated from the study						
Withdrawal form	To be completed whenever a patient withdraws from the study						
Death	To be completed whenever a patient dies						

Abbreviations: ABI, ankle brachial index; AC, anticoagulant treatment; CEAP, Clinical Etiological Anatomical Pathophysiology classification; CRF, case report form; F/U: follow-up; PTS, postthrombotic syndrome; QOL, quality of life; SAE, serious adverse event; VAS: visual analog scale; VTE, venous thromboembolism (deep vein thrombosis and/or pulmonary embolism).

^aPhone call follow-up simultaneous to the visit in person (±15 d).

contacted by phone at 15 days (±2 days), 6 months (±15 days), and 18 months (±15 days) to provide individual coaching on compliance, how to use ECS, and to check if they needed new ECS or needed to change the size. The data collected and examinations performed at each follow-up visit are summarized in Figure 1 and Table 2.

5.3 | Assessment of outcomes

5.3.1 | Primary outcome

The primary outcome, cumulative incidence of PTS at 2 years, was measured using the Villalta scale and PTS was considered as present if the score was ≥5 in the leg ipsilateral to the initial DVT, at a single assessment, either at the 1- or 2-year follow-up visit.^{6,65} Physical signs were assessed by investigators with the aid of a full-color visual guide, and symptoms were rated by the patients. All investigators received individual training on 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.⁶⁶ For

all patients with a Villalta score ≥5, the investigator assessed if there was a possible differential diagnosis besides CVI or PTS that could explain the Villalta score.

5.3.2 | Secondary outcomes

- Severity of PTS assessed using the Villalta score⁶⁵ was considered as mild, moderate, or severe if the score was 5-9, 10-14, and ≥ 15, respectively, or if a venous ulcer was present. PTS was also assessed with the Ginsberg method.⁶³
- Compliance to ECS was considered as optimal if patients (i) self-reported use of the allocated study ECS ≥80% of the overall time (based on the patient's diary, compliance was assessed weekly for 3 months and then monthly till the end of follow-up) and (ii) had a modified GIRERD score of 0-2.⁶⁷ The GIRERD score is a validated French tool to assess self-reported compliance and is derived from MORISKY score.⁶⁸ For this study, we removed a question corresponding to treatment renewal from the original GIRERD score; as in CELEST, patients automatically received their ECS at home. In subgroup analyses, compliance was defined as null, weak, reasonable (corresponding to the expected

compliance in routine clinical practice⁵¹) or good if self-reported use of ECS was 0%-19%, 20%-49%, 50%-79%, and ≥80% of time, respectively.

- QOL was assessed using validated general (EUROQUOLEQ5D-3L)⁶⁹ and chronic venous specific (CIVIQ)⁷⁰ questionnaires that were completed by the patients at each follow-up visit.
- Pain and edema discomfort were assessed using a 10-mm visual analog scale by the patient weekly for 3 months and then monthly until the end of follow-up. Edema was also assessed by the investigator at inclusion and each follow-up visit (Godet's sign and ankle perimeter). The presence of CVI was assessed by the investigator with the CEAP classification.⁷¹
- The following parameters were assessed to identify predictors of PTS: patients' characteristics (eg, age, sex, obesity), DVT extent, clot resolution on US (between baseline and 3 months), unprovoked character of DVT, time between onset of DVT symptoms and beginning of treatment, pain intensity at baseline (pain item of the Villalta score assessed in the leg ipsilateral to DVT), pain and edema during follow-up, and contralateral Villalta score at baseline.
- Serious adverse events including death, major bleeding, and VTE recurrence (as defined by the ISTH standards)^{72,73} as well as all other adverse events were recorded.
- The thrombus burden was assessed using the LET US classification^{74,75} and reflux in the common femoral, femoral, popliteal, fibular, and anterior and posterior tibial veins as well as the great saphenous veins was measured. Reflux was considered as being present if it is >1.0 seconds in deep veins and >0.5 seconds in superficial veins.

5.4 | Sample size calculation

In one of the open-label RCTs that compared 30-40 mm Hg ECS versus no ECS to prevent PTS after the first proximal DVT where the PTS was assessed with the Villalta score, as in CELEST, 25% of patients assigned to the 30-40 mm Hg ECS group developed PTS after 2 years.¹² In this previous study, PTS was considered to be present if the Villalta score was ≥5 at two consecutive assessments, and patients underwent five PTS assessments. This is at variance from CELEST, where one positive assessment will be sufficient to consider that PTS is present as per guidelines,⁶⁵ and patients underwent two assessments. We therefore estimated that the rate of PTS would be about 25% in the 35 mm Hg group in our study. In the absence of available data and given that most of the detected PTS cases were expected to be mild,¹² the predefined noninferiority margin for the difference in success rates was set at 12.5%. This margin was set by the CELEST Scientific Committee, in consideration of the non-life-threatening character of the primary outcome. At a one-sided significance level of 0.05 and a power of 80%, it was calculated that 296 patients would be needed. Taking into consideration the loss to follow-up and death that were expected to be <15% (12.2% at 3 years in the open-label trial),¹² we planned to include 350 patients (175 per treatment group).

5.5 | Statistical analysis

Data will be analyzed once, at the end of follow-up, except for data on patients' self-reported pain and edema discomfort, which will be assessed at 3 months. Intention-to-treat analyses, which include all randomized patients after exclusion of any that were ineligible, will be used for all outcomes. To test the hypothesis of superiority of 35 versus 25 mm Hg in the prevention of PTS, per-protocol analyses will be done among compliant patients without major protocol deviation using two different definitions of compliance (optimal and reasonable as defined in Assessment of Outcomes section).

Descriptive statistics for baseline variables will be done to describe the baseline status of the treatment groups. Losses to follow-up, withdrawals, and deaths will be censored at last date of follow-up.

The primary outcome is the cumulative rate of PTS at 2 years at the 1- or 2-year follow-up visit. We will calculate the 90% confidence interval for the difference in the rates of PTS between the 25 versus 35 mm Hg groups. Noninferiority will be concluded if the upper limit of this confidence interval is <12.5%. We will also do two one-sided test with calculation of the *P* value associated with a one-tailed null hypothesis H_0 : difference ≥ 12.5%.⁷⁶ We will then test the superiority of the 25 mm Hg ECS compared with the 35 mm Hg ECS, as per the protocol amendment.

For the primary outcome, there will be two separate analyses: one based on all available data, and one in which missing data will be replaced by self-reported Villalta score, if available, or by a multivariable model including known risk factors for PTS. To compare the rates of PTS between groups (overall rate and among compliant patients), chi-square or Fisher exact tests will be used.

For qualitative secondary outcomes (rates of patients compliant to ECS, with edema, with PTS according to the Ginsberg method, with trophic changes, with deep or superficial reflux or with residual obstruction on US), we will use chi-square or Fisher exact tests, as appropriate.

For quantitative secondary outcomes, we will assess evolution over time (M3-M12-M24) of results for the CIVIQ20 and EUROQOL questionnaires, as well as for pain and edema in both groups using mixed-design models with presentation of *P* value associated with the time*treatment interaction.

Student *t* tests or Mann-Whitney tests will be used to compare leg volume, Villalta score (continuous), and US data at 24 months.

Kaplan-Meier analyses will be used to calculate the cumulative incidence of PTS. To assess prognostic factors for PTS, we will use Cox models and include variables mentioned in the Assessment of Outcomes section, with anticoagulant treatment entered as a time-dependent variable. Based on the number of reported events, we will also calculate the cumulative rates of death, VTE recurrence, and major bleeding.

Other analyses not scheduled in the protocol may be decided by scientific committee.

Analyses will be done with STATA 15.0 (StataCorp, College Station, TX, USA). For all analyses, a two-sided *P* value of ≤ 0.05 will be considered significant.

5.6 | Data management

Data will be entered online at trial sites using standardized case report forms and a customized web-based data entry tool. Data quality will be ensured via the use of validation checks at the time of data entry. Data will be reviewed and cleaned by the database coordinator on an ongoing basis by initiating and following up on queries to the sites. Data management will be overseen by the trial coordinating center. At the end of the trial, all data will be completely monitored.

5.7 | Ethical considerations

The CELEST trial protocol was approved by the South East II Ethics Committee (Lyon, France) in November 2011 (Number 2011-032) and registered on ClinicalTrials.gov (NCT01578122). Written informed consent was obtained from all participating patients.

6 | DISCUSSION

The efficacy of ECS to prevent PTS after DVT is uncertain and debated, with conflicting conclusions from published meta-analyses. Guidelines, even sometimes those issued in the same country, have heterogeneous recommendations. For example, in France, where the CELEST trial is conducted, one guideline recommends ECS for the prevention of PTS after DVT, and another one does not.^{18,21} Differences in results for ECS efficacy for PTS prevention between studies may be due to a placebo effect or suboptimal compliance.

The CELEST study may provide important evidence for the efficacy of ECS to prevent PTS. The study was designed to minimize the main potential limitations of previously published studies, that is, open-label design (placebo effect) and compliance to ECS.

CELEST is a double-blind RCT, and as both study ECS are tighter than placebo ECS or even thromboembolic deterrent stockings, there is less chance that patients will guess which ECS they were allocated. All ECS were specifically manufactured by Innothra (Arcueil, Ile-de-France) for the purpose of the study and were fully anonymized (no distinctive sign such as a label or a seam). Furthermore, to confirm the quality of masking, patients will be asked to state at the end of the study which treatment they thought they had been assigned to receive: 25 mm Hg ECS, 35 mm Hg ECS, or uncertain.

Regarding compliance, the following actions were taken to optimize it: (i) large choice of ECS models in terms of length, color, open- or closed-toe that could be changed at any time; (ii) regular and frequent patient education and coaching actions during the course of the study. Finally, to improve compliance reporting, we will not only use prospectively maintained diaries (current gold standard),⁵¹ but we will also use a stricter definition

of compliance to limit the risk of patient overestimation by adding the GIRERD scale to the classical ECS compliance self-reported assessment.⁶⁷

The expected results from the CELEST trial could be interpreted as follow:

- If the 25 mm Hg ECS are found to be noninferior to the 35 mm Hg ECS, then they could be used to prevent PTS if one believes, despite SOX trial negative results, that ECS are useful to prevent PTS.¹³
- If the 25 mm Hg ECS are not noninferior to the 35 mm Hg ECS and the 35 mm Hg ECS are found to be superior, this will challenge SOX trial results as it will suggest that ECS are efficacious in the prevention of PTS and that the highest strength provides a better outcome via a dose-effect mechanism.
- If the 25 mm Hg ECS are more efficacious than the 35 mm Hg ECS and are associated with better compliance, this will suggest that ECS are efficacious for the prevention of PTS and the lack of efficacy reported in the SOX trial could be due to suboptimal compliance.

The CELEST results will also be interpreted in light of new results from the OCTAVIA (Optical Coherence Tomography Assessment of Gender Diversity in Primary Angioplasty), CANANO, and IDEAL-DVT trials^{64,77,78} that suggest that use of below-knee ECS should be favored because they are associated with fewer side effects than thigh-length ECS and that patients could stop wearing ECS as early as 6 months after their acute DVT if they have two consecutive Villalta scores that are <5.

7 | CONCLUSION

The efficacy of ECS to prevent PTS is uncertain and ECS are no longer recommended in some international guidelines. The heterogeneous trial results could be due to a placebo effect or suboptimal compliance. The ongoing double-blind CELEST RCT that compares high- versus lower-strength ECS was designed to improve compliance to ECS and should contribute to improve our knowledge on the efficacy of ECS to prevent PTS. The results from CELEST will be interpreted in the light of other recently published RCTs that assessed the efficacy of ECS to prevent PTS.

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AUTHOR CONTRIBUTIONS

Conception and design of the manuscript: JPG and JLB; funding: IB, and FV; data acquisition and analysis: all authors; drafting of the article: JPG; critical revision for important intellectual content: all authors; final approval of the manuscript: all authors.

RELATIONSHIP DISCLOSURE

JPG received a travel grant from Innothera to present the study. All other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

JPG takes responsibility for the content of this manuscript.

REFERENCES

- Makedonov SR, Kahn JP. Galanaud, Prevention and management of the post thrombotic syndrome. *J Clin Med*. 2020;9(4):923.
- Galanaud JP, Monreal M, Kahn SR. Epidemiology of the post-thrombotic syndrome. *Thromb Res*. 2018;164:100–9.
- Prandoni P, Kahn SR. Post-thrombotic syndrome: prevalence, prognostication and need for progress. *Br J Haematol*. 2009;145:286–95.
- Rabinovich A, Kahn SR. How I treat the postthrombotic syndrome. *Blood*. 2018;131:2215–22.
- Ten Cate-Hoek AJ. Prevention and treatment of the post-thrombotic syndrome. *Res Pract Thromb Haemost*. 2018;2:209–19.
- Kahn SR, Comerota AJ, Cushman M, Evans NS, Ginsberg JS, Goldenberg NA, et al. The postthrombotic syndrome: evidence-based prevention, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation*. 2014;130:1636–61.
- Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e419S–e496S.
- Galanaud JP, Laroche JP, Righini M. The history and historical treatments of deep vein thrombosis. *J Thromb Haemost*. 2013;11:402–11.
- Clinical Guideline, Quality standard for diagnosis and management of venous thromboembolic diseases. National Institute for Health and Care Excellence, DOI (2012) Clinical guideline [CG144].
- Mismetti P, Baud JM, Becker F, Belmahdi F, Blanchard P, Constans J, et al. Guidelines for good clinical practice: prevention and treatment of venous thromboembolism in medical patients. *J Mal Vasc*. 2010;35:127–36.
- Brandjes DP, Buller HR, Heijboer H, Huisman MV, de Rijk M, Jagt H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet*. 1997;349:759–62.
- Prandoni P, Lensing AW, Prins MH, Frulla M, Marchiori A, Bernardi E, et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. *Ann Intern Med*. 2004;141:249–56.
- Kahn SR, Shapiro S, Wells PS, Rodger MA, Kovacs MJ, Anderson DR, et al. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. *Lancet*. 2014;383:880–8.
- Amin EE, Bistervels IM, Meijer K, Tick LW, Middeldorp S, Mostard G, et al. Reduced incidence of vein occlusion and postthrombotic syndrome after immediate compression for deep vein thrombosis. *Blood*. 2018;132:2298–304.
- Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest*. 2016;149:315–52.
- ten Cate-Hoek AJ. Elastic compression stockings—is there any benefit? *Lancet*. 2014;383:851–3.
- NICE guideline, Venous thromboembolic diseases: diagnosis, management and thrombophilia testing NICE guideline [NG158], DOI (2020) <https://www.nice.org.uk/guidance/ng158>
- Sanchez O, Benhamou Y, Bertolotti L, Constans J, Couturaud F, Delluc A, et al. Recommendations for best practice in the management of venous thromboembolic disease in adults. Long version. *Rev Mal Respir*. 2019;36(2):249–283. <https://doi.org/10.1016/j.rmr.2019.01.003>
- Rabe E, Partsch H, Hafner J, Lattimer C, Mosti G, Neumann M, et al. Indications for medical compression stockings in venous and lymphatic disorders: an evidence-based consensus statement. *Phlebology*. 2018;33:163–84.
- Aloi TL, Camporese G, Izzo M, Kontothanassis D, Santoliquido A. Refining diagnosis and management of chronic venous disease: outcomes of a modified Delphi consensus process. *Eur J Intern Med*. 2019;65:78–85.
- Quérel A, Elias M, Maufus M, Elias MA, Sevestre JP, Galanaud JL, et al. Unresolved questions on venous thromboembolic disease. Consensus statement of the French Society for Vascular Medicine (SFMV). *J Med Vasc*. 2019;44:e1–e47.
- Jayaraj M. Meissner, Impact of graduated compression stockings on the prevention of post-thrombotic syndrome - results of a randomized controlled trial. *Phlebology*. 2015;30:541–8.
- Avila ML, Montoya M, Lumia C, Marson A, Brandao LR, Tomlinson G. Compression stockings to prevent post-thrombotic syndrome in adults, a Bayesian meta-analysis. *Thromb Res*. 2019;182:20–6.
- Tie HT, Luo MZ, Luo MJ, Li K, Li Q, Wu QC. Compression therapy in the prevention of postthrombotic syndrome: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2015;94:e1318.
- Skervin AL, Thapar A, Franchini AJ, Prandoni P, Shalhoub J, Davies AH. Systematic review and meta-analysis of utility of graduated compression stockings in prevention of post-thrombotic syndrome. *Eur J Vasc Endovasc Surg*. 2016;51:838–45.
- Burgstaller JM, Steurer J, Held U, Amann-Vesti B. Efficacy of compression stockings in preventing post-thrombotic syndrome in patients with deep venous thrombosis: a systematic review and metaanalysis. *Vasa*. 2016;45:141–7.
- Jin YW, Ye H, Li FY, Xiong XZ, Cheng NS. compression stockings for prevention of postthrombotic syndrome: a systematic review and meta-analysis. *Vasc Endovascular Surg*. 2016;50:328–34.
- Berntsen CF, Kristiansen A, Akl EA, Sandset PM, Jacobsen EM, Guyatt G, et al. Compression stockings for preventing the post-thrombotic syndrome in patients with deep vein thrombosis. *Am J Med*. 2016;129(4):447.e1–447.e20.
- Appelen D, van Loo E, Prins MH, Neumann MH, Kolbach DN. Compression therapy for prevention of post-thrombotic syndrome. *Cochrane Database Syst Rev*. 2017;CD004174.
- Subbiah R, Aggarwal V, Zhao H, Kolluri R, Chatterjee S, Bashir R. Effect of compression stockings on post thrombotic syndrome in patients with deep vein thrombosis: a meta-analysis of randomised controlled trials. *Lancet Haematol*. 2016;3:e293–e300.
- Eberhardt RT, Raffetto JD. Chronic venous insufficiency. *Circulation*. 2014;130:333–46.
- Lattimer CR, Kalodiki E, Azzam M, Geroulakos G. Haemodynamic performance of low strength below knee graduated elastic compression stockings in health, venous disease, and lymphoedema. *Eur J Vasc Endovasc Surg*. 2016;52:105–12.
- Arpaia G, Cimminiello C, Mastrogiacomo O, de Gaudenzi E. Efficacy of elastic compression stockings used early or after resolution of the edema on recanalization after deep venous thrombosis: the COM.PRE Trial. *Blood Coagul Fibrinolysis*. 2007;18:131–7.
- Blattler W, Partsch H. Leg compression and ambulation is better than bed rest for the treatment of acute deep venous thrombosis. *Int Angiol*. 2003;22:393–400.
- Boehler K, Kittler H, Stolkovich S, Tzaneva S. Therapeutic effect of compression stockings versus no compression on isolated superficial vein thrombosis of the legs: a randomized clinical trial. *Eur J Vasc Endovasc Surg*. 2014;48:465–71.

36. Murphy MA, Joyce WP, Condrón C, Bouchier-Hayes D. A reduction in serum cytokine levels parallels healing of venous ulcers in patients undergoing compression therapy. *Eur J Vasc Endovasc Surg.* 2002;23:349–52.
37. Cooley BC, Chen CY, Hess R, Schmeling G. Incomplete resolution of deep vein thrombosis under reduced flow conditions. *Thromb Res.* 2013;131:55–8.
38. Tavel ME. The placebo effect: the good, the bad, and the ugly. *Am J Med.* 2014;127:484–8.
39. Dimond EG, Kittle CF, Crockett JE. Comparison of internal mammary artery ligation and sham operation for angina pectoris. *Am J Cardiol.* 1960;5:483–6.
40. Kaptchuk TJ, Kelley JM, Conboy LA, Davis RB, Kerr CE, Jacobson EE, et al. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. *BMJ.* 2008;336:999–1003.
41. Roche-Nagle G, Ward F, Barry M. Current prescribing patterns of elastic compression stockings post-deep venous thrombosis. *Phlebology.* 2010;25:72–8.
42. Carolyn C. Post-thrombotic syndrome patient education based on the health belief model: self-reported intention to comply with recommendations. *J Wound Ostomy Continence Nurs.* 2011;38:648–54.
43. Dawson AJ, Akaberi A, Galanaud JP, Morrison DR, Kahn SR. Patient-reported reasons for and predictors of noncompliance with compression stockings in a randomized trial of stockings to prevent postthrombotic syndrome. *Res Pract Thromb Haemost.* 2020;4:269–77.
44. Bouman AC, Ten Cate-Hoek AJ, Dirksen CD, Joore MA. Eliciting patients' preferences for elastic compression stocking therapy after deep vein thrombosis: potential for improving compliance. *J Thromb Haemost.* 2016;14:510–7.
45. Perrin M, Eklof B. Does prescription of medical compression prevent development of post-thrombotic syndrome after proximal deep venous thrombosis? *Phlebology.* 2016;31:160–9.
46. Raju S, Hollis K, Neglen P. Use of compression stockings in chronic venous disease: patient compliance and efficacy. *Ann Vasc Surg.* 2007;21:790–5.
47. Delluc C, Gouedard L, De Saint Martin C, Garcia AM, Roguedas L, Bressollette L, et al. Incidence, risk factors and skin manifestations of post-thrombotic syndrome: a four-year follow-up of patients included in the EDITH study. *Rev Med Interne.* 2010;31:729–34.
48. Kayssi A, Petrosioniak J, Levenstadt N, Eisenberg S, Jenkins G, Roche-Nagle, Rates of elastic compression stockings prescription following the diagnosis of deep venous thrombosis among Canadian emergency physicians and trainees. *CJEM.* 2015;17:248–52.
49. Kahn SR, Elman E, Rodger MA, Wells PS. Use of elastic compression stockings after deep venous thrombosis: a comparison of practices and perceptions of thrombosis physicians and patients. *J Thromb Haemost.* 2003;1:500–6.
50. Uhl JF, Benigni JP, Chahim M, Frederic D. Prospective randomized controlled study of patient compliance in using a compression stocking: Importance of recommendations of the practitioner as a factor for better compliance. *Phlebology.* 2018;33:36–43.
51. Kankam HKN, Lim CS, Fiorentino F, Davies AH, Gohel MS. A summation analysis of compliance and complications of compression hosiery for patients with chronic venous disease or post-thrombotic syndrome. *Eur J Vasc Endovasc Surg.* 2018;55:406–16.
52. Suehiro K, Morikage N, Yamashita O, Harada T, Ueda K, Samura M, et al. Adherence to and efficacy of different compression methods for treating chronic venous insufficiency in the elderly. *Phlebology.* 2016;31:723–8.
53. Labropoulos N, Gasparis AP, Caprini JA, Partsch H. Compression stockings to prevent post-thrombotic syndrome. *Lancet.* 2014;384:129–30.
54. Roumen-Klappe EM, den Heijer M, van Rossum J, Wollersheim H, van der Vleuten C, Thien T, et al. Multilayer compression bandaging in the acute phase of deep-vein thrombosis has no effect on the development of the post-thrombotic syndrome. *J Thromb Thrombolysis.* 2009;27:400–5.
55. Kahn SR, Shapiro S, Ginsberg JS. Compression stockings to prevent post-thrombotic syndrome - Authors' reply. *Lancet.* 2014;384:130–1.
56. Keeling D. Stockings to prevent post-thrombotic syndrome-where are we now? *Lancet Haematol.* 2018;5:e4–e5.
57. Wakefield TW, Obi AT, Henke PK. Elastic compression stockings: the jury is still out. *Lancet Haematol.* 2016;3:e262–e263.
58. Ouvry P, Arnoult AC, Genty C, Galanaud JP, Bosson JL. Compression therapy and deep-vein thrombosis: a clinical practice survey. *J Mal Vasc.* 2012;37:140–5.
59. Wittkowsky AK, Nutescu EA, Devine EB. Compression stockings to prevent post-thrombotic syndrome: a role for anticoagulation clinics? *J Thromb Thrombolysis.* 2008;26:248–50.
60. Flour M, Clark M, Partsch H, Mosti G, Uhl JF, Chauveau M, et al. Dogmas and controversies in compression therapy: report of an International Compression Club (ICC) meeting, Brussels. *Int Wound J.* 2011;10(2013):516–26.
61. Mosti G, Partsch H. High compression pressure over the calf is more effective than graduated compression in enhancing venous pump function. *Eur J Vasc Endovasc Surg.* 2012;44:332–6.
62. Galanaud JP, Holcroft CA, Rodger MA, Kovacs MJ, Betancourt MT, Wells PS, et al. Comparison of the Villalta post-thrombotic syndrome score in the ipsilateral vs. contralateral leg after a first unprovoked deep vein thrombosis. *J Thromb Haemost.* 2012;10:1036–42.
63. Ginsberg JS, Hirsh J, Julian J, Vander LaandeVries M, Magier D, MacKinnon B, et al. Prevention and treatment of postphlebotic syndrome: results of a 3-part study. *Arch Intern Med.* 2001;161:2105–9.
64. Prandoni P, Noventa F, Quintavalla R, Bova C, Cosmi B, Siragusa S, et al. Thigh-length versus below-knee compression elastic stockings for prevention of the postthrombotic syndrome in patients with proximal-venous thrombosis: a randomized trial. *Blood.* 2012;119:1561–5.
65. Kahn SR, Partsch H, Vedantham S, Prandoni P, Kearon C. Definition of post-thrombotic syndrome of the leg for use in clinical investigations: a recommendation for standardization. *J Thromb Haemost.* 2009;7:879–83.
66. Utne KK, Ghanima W, Foyen S, Kahn S, Sandset PM, Wik HS. Development and validation of a tool for patient reporting of symptoms and signs of the post-thrombotic syndrome. *Thromb Haemost.* 2016;115:361–7.
67. Girerd X, Hanon O, Anagnostopoulos K, Ciupek C, Mourad JJ, Consoli S. Assessment of antihypertensive compliance using a self-administered questionnaire: development and use in a hypertension clinic. *Presse Med.* 2001;30:1044–8.
68. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care.* 1986;24:67–74.
69. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med.* 2001;33:337–43.
70. Launois R, Reboul-Marty J, Henry B. Construction and validation of a quality of life questionnaire in Chronic Lower Limb Venous Insufficiency (CIVIQ). *Qual Life Res.* 1996;5:539–54.
71. Eklof RB, Rutherford JJ, Bergan PH, Carpentier P, Gloviczki RL, Kistner MH, et al. Wakefield, Revision of the CEAP classification for chronic venous disorders: consensus statement. *J Vasc Surg.* 2004;40:1248–52.
72. Ageno W, Squizzato A, Wells PS, Buller HR, Johnson G. The diagnosis of symptomatic recurrent pulmonary embolism and deep vein thrombosis: guidance from the SSC of the ISTH. *J Thromb Haemost.* 2013;11:1597–602.

73. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S, Subcommittee on Control of Anticoagulation. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. *J Thromb Haemost*. 2015;13:2119–26.
74. Bosson JL, Riachi M, Pichot O, Michoud E, Carpentier PH, Franco A. Diameters of acute proximal and distal deep venous thrombosis of the lower limbs. *Int Angiol*. 1998;17:260–7.
75. Strijkers RH, Arnoldussen CW, Wittens CH. Validation of the LET classification. *Phlebology*. 2015;30:14–9.
76. Schuirmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J Pharmacokinet Biopharm*. 1987;15:657–80.
77. Mol GC, van de Ree MA, Klok FA, Tegelberg MJ, Sanders FB, Koppen S, et al. One versus two years of elastic compression stockings for prevention of post-thrombotic syndrome (OCTAVIA study): randomised controlled trial. *BMJ*. 2016;353:i2691.
78. Ten Cate-Hoek AJ, Amin EE, Bouman AC, Meijer K, Tick LW, Middeldorp S, et al. Individualised versus standard duration of elastic compression therapy for prevention of post-thrombotic syndrome (IDEAL DVT): a multicentre, randomised, single-blind, allocation-concealed, non-inferiority trial. *Lancet Haematol*. 2018;5:e25–e33.

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