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Value of a Planned Compression Ultrasonography after an Isolated Superficial Vein Thrombosis: Results from a Prospective Multicentre Study

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ABSTRACT

Objectives: To assess the efficiency of a systematically planned compression ultrasonography (SP-CUS) to detect venous thrombotic complications (VTCs) in patients with symptomatic isolated superficial vein thrombosis (SVT).
Design: Post hoc analysis of a prospective, multicentre, cohort study (POST).
Patients: As many as 537 patients with CUS-confirmed isolated SVT undergoing an SP-CUS 8–15 days after the initial CUS.
Outcomes: Asymptomatic VTC (extension or recurrence of SVT, deep-vein thrombosis (DVT) of the lower limbs) diagnosed by the SP-CUS and symptomatic thromboembolic complications (VTC and pulmonary embolism (PE)) up to 3 months.
Results: VTC was suspected before or on the day of the SP-CUS in 18 patients (3.0%). Among the 519 asymptomatic patients (97%) undergoing SP-CUS, this revealed asymptomatic VTC in 12 patients (2.3%; 4 DVT, 4 SVT recurrences, 4 SVT extensions), none of whom subsequently experienced symptomatic thromboembolic events up to 3 months. Among the 507 patients with a normal SP-CUS, 29 (5.7%) presented symptomatic thromboembolic events during follow-up: 2 PE, 7 DVT, 9 SVT recurrences and 11 SVT extensions.
Conclusions: In this study, the SP-CUS detected a few asymptomatic VTC, but failed to identify patients at risk of thromboembolic events during follow-up. Use of an SP-CUS was therefore neither efficient nor cost effective.

Superficial vein thrombosis (SVT) of the lower limbs is a common disease, affecting 3–11% of the general population.[1–3] SVT may be associated with a deep-vein thrombosis (DVT) or isolated. The incidence of extension to the deep venous system after an isolated SVT is poorly known.[4–6] In their article published in 2005, Leon et al.[1] emphasise that "patients with SVT require follow-up, either clinical or with duplex ultrasonography. Compression ultrasonography (CUS) should be performed at about 7–10 days after the original diagnosis to assess the extent and progression of SVT". The recent CALISTO study[7] assessed the efficacy and safety of fondaparinux in the treatment of symptomatic, isolated SVT. It has shown that the risk of symptomatic thromboembolic complications or death was reduced by the administration of a daily dose of 2.5 mg of fondaparinux for 45 days. Until these results became available, the grade of evidence for the antithrombotic treatments proposed in published guidelines was low[8] and several management strategies were indicated, comprising various combinations of treatment, clinical follow-up and a systematic ultrasonographic examination during follow-up.[9–14]

CUS is a quite easily performed and non-invasive imaging examination, but the systematic use of a follow-up CUS to screen asymptomatic patients remains controversial. The low event rate in

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the placebo group of the CALISTO study, in which no systematically planned CUS (SP-CUS) was envisaged, calls into question the relevance of performing such an examination. Our objective was to evaluate the efficiency of an SP-CUS in patients with isolated SVT.

Material and Methods

Patients

We performed a *post hoc* analysis of data obtained in the POST study, a national, multicentre, observational prospective study of patients with SVT confirmed by CUS. The design and results of this study have been described in detail elsewhere.[15] In brief, patients older than 18 years with a symptomatic lower-limb SVT at least 5 cm long on CUS were considered for inclusion. Patients who had undergone surgery under general or loco-regional anaesthesia in the previous 10 days, those in whom SVT had occurred after sclerotherapy within the previous 30 days, and those whose follow-up was not considered to be feasible, were excluded.

Out of the 600 consecutive patients with objectively confirmed isolated SVT of the lower limbs included in POST,[15] we excluded patients in whom SP-CUS was not performed and patients who underwent the SP-CUS before day 8 or after day 15. Then, our study population consisted of the 537 patients who had undergone a comprehensive SP-CUS of both lower limbs, including the distal and proximal deep veins, between 8 and 15 days after the initial CUS. The study was conducted in accordance with the Declaration of Helsinki (Hong Kong amendment), Good Clinical Practice (European Guidelines) and relevant French legal and regulatory requirements. The protocol was approved by the local Ethics Committee (Centre Hospitalo-Universitaire, Saint-Etienne, France). Oral informed consent was obtained from all subjects analysed.

Study outcomes

All patients underwent a comprehensive CUS of both lower limbs (including proximal and distal deep veins) at entry into the study. A second CUS was systematically planned between day 8 and day 15. The ultrasound assessment was based on a complete CUS protocol performed and interpreted by vascular medicine physicians having at least 2 years of experience with ultrasound. Using an adequate set of probes, the proximal veins were examined in supine or in semi-upright position and the distal veins (including calf muscular veins) were examined in a sitting position. The great and small saphenous veins were also examined. The main diagnostic criterion was the compressibility of the vein in the transverse cross-sectional view by pressing with the probe on the vein at 1–3 cm(s) intervals all along the vein under investigation. Pulsed Doppler was performed in common femoral veins (CFVs) and in popliteal veins. Normal and symmetrical breath-induced modulations of the flow in CFV were considered as exclusion criterion for ilio-caval DVT when the direct US examination of the ilio-caval veins was not accurate enough. Colour Doppler flow imaging, grey-scale imaging of the vein in longitudinal view and thrombus imaging were used as part of the US examination or as secondary criterion, not as main criterion for diagnosis of vein thrombosis. Patients were also asked to undergo a further CUS in the event of new symptoms or signs in the lower limbs during the 3-month follow-up. The primary clinical outcomes were asymptomatic venous thrombotic events (extension or recurrence of SVT, DVT of the lower limbs) diagnosed by the SP-CUS. The secondary outcomes were symptomatic thromboembolic events (extension or recurrence of SVT, DVT of the lower limbs and pulmonary embolism (PE)) up to 3 months. DVT was confirmed by CUS or contrast phlebography. DVT was defined as distal DVT when located in the calf, not extended into the popliteal vein and as proximal otherwise. PE was confirmed by high-probability ventilation–perfusion scan or positive helical computed tomography scan, or at autopsy. Extension or recurrence of SVT was confirmed by CUS. Recurrence of SVT was defined as the occurrence of a new SVT, distinct from the initial thrombotic event, occurring either in a different superficial vein from that implicated in the qualifying event, or in the same vein but clearly differentiated from the initial qualifying event by the presence of an intervening open venous segment. Extension of SVT was defined as a proximal extension of SVT by more than 5 cm on CUS.

All events diagnosed as symptomatic thromboembolic events within the 3-month follow-up period were centrally adjudicated by an independent committee with respect to their symptomatic or asymptomatic nature. Only confirmed symptomatic events were retained.

Patients were considered to present an asymptomatic venous thrombotic event between day 8 and day 15 if the SP-CUS was positive and no symptomatic thromboembolic event had been notified before or on the day of the SP-CUS.

The therapeutic management of patients was not standardised. All new medical and surgical treatments prescribed since inclusion was recorded at the 8–15-day and 3-month follow-up visits.

Data analysis

Qualitative data were reported as numbers and percentages. Quantitative data were reported as median values with first quartile (Q1) and third quartile (Q3). SAS software, version 9.1 (SAS Institute, Cary, North Carolina, USA) was used to analyse and process all data.

Results

Population characteristics

A total of 600 consecutive patients with objectively confirmed SVT of the lower limbs was included in the initial cohort. SP-CUS was not performed in 24 patients and 39 patients underwent the SP-CUS before day 8 or after day 15. Finally, a total of 537 patients with an isolated SVT underwent the SP-CUS. Their demographic and clinical characteristics are shown in Table 1. The median age of

Table 1
Patient characteristics at inclusion.

Variable	Isolated SVT ($N = 537$)
Median age (IQR), y	61 (48–73)
Age ≥75 years, *n* (%)	111 (20.7%)
Women, *n* (%)	387 (64.5)
Median body mass index (IQR), kg/m^2	27.3 (24–30)
BMI > 30 kg/m^2, *n* (%)	159 (29.6%)
Interval between symptom onset and diagnosis	
Median interval (IQR), d	5.0 (3–10)
>7 d, *n* (%)	198 (38.4)
Risk factors, *n* (%)	
Varicose veins	467 (87.0%)
History of venous thromboembolism	
SVT	189 (35.2%)
DVT or PE	101 (18.8%)
Family history	172 (32.0%)
Cancer	
Active	18 (3.4%)
Previous	25 (4.7%)
Permanent immobility	28 (5.2%)
Chronic cardiac or respiratory insufficiency	27 (5.0%)
Known biological thrombophilia	28 (5.2%)
Autoimmune disease	6 (1.1%)

Percentages are calculated on the basis of available data. IQR = interquartile range; DVT = deep-vein thrombosis; PE = pulmonary embolism; SVT = superficial venous thrombosis.

the patients was 61 years (interquartile range (IQR), 48–73 years), 111 (21%) were at least 75 years old, 159 (30%) were obese (BMI >30 kg m^{-2}) and 349 (65%) were women.

Results of the SP-CUS and 3-month follow-up

A symptomatic thromboembolic event was suspected before or on the day of the SP-CUS in 18 patients (3.0%). This was confirmed in 11 patients (four DVT, one recurrence of SVT and six proximal extensions of SVT). Among the 519 asymptomatic patients (97%) undergoing the SP-CUS, 12 (2.3%) were found to have experienced an asymptomatic venous thrombotic event. Four of these events comprised distal DVT, four were recurrences of SVT and four were proximal extensions of SVT ranging from 5 to 14 cm (Fig. 1). No symptomatic thromboembolic event was recorded at 3 months in any of these 12 patients.

Among the 507 patients with a normal SP-CUS, 29 (5.7%) experienced a symptomatic thromboembolic event during the follow-up. Two patients presented a PE and seven patients presented a DVT (four distal and three proximal). The other 20 patients presented a recurrent SVT or an extension of the initial SVT.

Pattern of therapeutic management before and after SP-CUS according to SP-CUS findings

Before SP-CUS, 440 (85%) of the 519 asymptomatic patients received anticoagulant treatment (in the form of heparin, heparin derivatives or a vitamin K agonist) between the initial diagnosis of SVT and the SP-CUS. Eleven of the 12 patients (92%) in whom the SP-CUS revealed an asymptomatic venous thrombotic event received an anticoagulant treatment versus 429 of the 507 patients (85%), showing no asymptomatic venous thrombotic event (Table 2).

Among the 12 patients with an asymptomatic venous thrombotic event revealed by the SP-CUS, the initial treatment remained unchanged in eight patients (67%) who were already receiving an anticoagulant. Finally, 9 (75%) of the 12 patients received an anticoagulant treatment after SP-CUS.

Table 2
Treatment before and after initial follow-up SP-CUS.

Variable	Negative CUS ($N = 507$)	Positive CUS ($N = 12$)
Treatment before SP-CUS		
Anticoagulant treatment	429 (84.6%)	11 (91.7%)
at therapeutic doses	291	7
at prophylactic doses	138	4
NSAID or antiplatelet agent	38 (7.5%)	0
Venotonic drugs, graduated compression stockings or surgery	25 (4.9%)	1 (8.3%)
No treatment	15 (3.0%)	0
No treatment change after SP-CUS	149 (29.4%)	8 (66.7%)
Anticoagulant at therapeutic doses	85	7
Anticoagulant at prophylactic doses	29	1
NSAID or antiplatelet agent	7	0
Venotonic drugs, graduated compression stockings or surgery	17	0
No treatment	11	0
Change of treatment after SP-CUS	358 (70.6%)	4 (33.3%)
Anticoagulant treatment (at therapeutic or prophylactic doses)	16	1
NSAID or antiplatelet agent	28	
Venotonic drugs, graduated compression stockings or surgery	217	3
No treatment	97	0

SP-CUS = systematically planned compression ultrasonography, NSAID = nonsteroidal anti-inflammatory drug.

Regarding the 507 patients showing no asymptomatic venous thrombotic event on SP-CUS, the initial treatment changed in 358 (71%) patients. Anticoagulant treatment was discontinued in 315 (73%) of the 429 patients with anticoagulant treatment before SP-CUS. After the SP-CUS, when treatment was changed, it was purely discontinued in 97 (27%) patients. Among the 29 patients who experienced a symptomatic thromboembolic event at 3 months, 28 were receiving an antithrombotic drug at the time of the SP-CUS. Only 11 of these patients continued to receive anticoagulant treatment after SP-CUS.

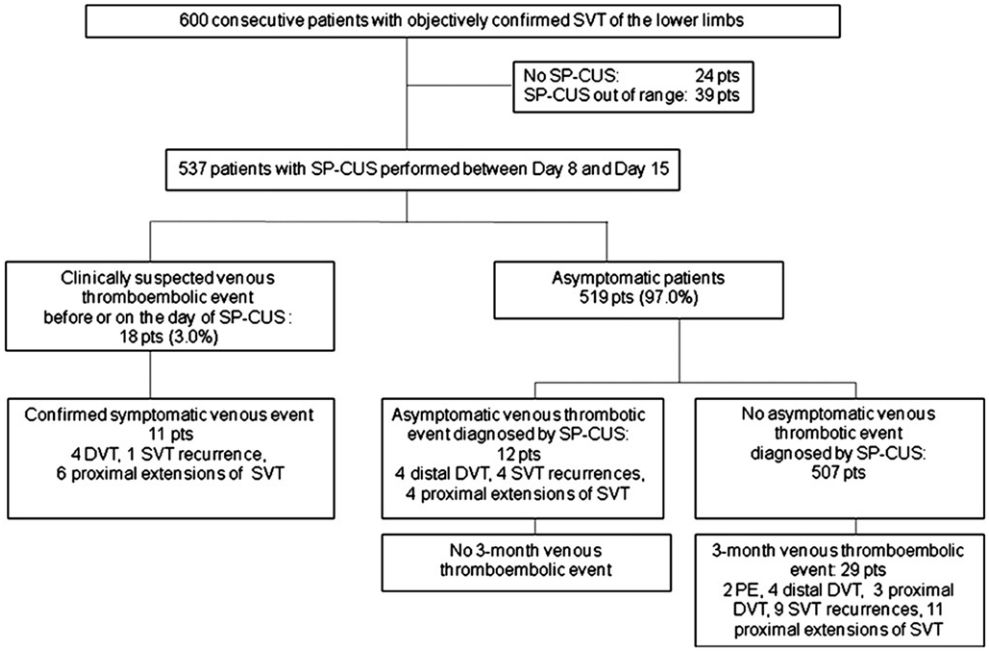

Figure 1. Study flow chart. DVT = deep-vein thrombosis; PE = pulmonary embolism; pts = patients; SP-CUS = systematically planned compression ultrasonography; SVT = superficial venous thrombosis.

Efficiency of the initial follow-up SP-CUS

A total of 52 patients experienced a thromboembolic event, either symptomatic or asymptomatic, from inclusion until the end of the 3-month follow-up. Twelve of these events were asymptomatic venous thrombotic events and were identified by the SP-CUS. The sensitivity of the SP-CUS is therefore 23%. The remaining 40 were symptomatic events: 11 occurred before or on the day of the SP-CUS and 29 occurred after the SP-CUS. These 29 events (56%) were not and could not have been detected by the SP-CUS.

Discussion

This is the first study to assess the clinical relevance of performing an SP-CUS during the follow-up of patients with SVT. We concentrated on patients who underwent a CUS between day 8 and day 15 without prior symptoms of thromboembolic events following the initial SVT.

By detecting asymptomatic venous thrombotic events, an SP-CUS would be relevant if it helped to differentiate high-risk and low-risk patients or if it led to an appropriate treatment modification.

In this study, only a few asymptomatic venous thrombotic events were detected by SP-CUS (12/519, 2.3%). Among these 12 events, 4 were DVT, all distal. None of these 12 patients experienced a further symptomatic event.

We cannot be sure what the outcome of these asymptomatic events would have been without the SP-CUS, but we may postulate that they would have become symptomatic. However, even if this hypothesis was correct, the SP-CUS failed to predict all the cases of symptomatic thromboembolic events occurring up to 3 months, missing 29 (56%) of the 52 venous thromboembolic events actually recorded at this time.

Hence, the SP-CUS failed to fully identify patients at risk of thromboembolic events during the follow-up, possibly because it led to inappropriate treatment modifications.

The clinical relevance and cost-effectiveness of performing an SP-CUS appear to be questionable. This is reflected by the pattern of therapeutic management following the SP-CUS. In most cases, detection of an asymptomatic venous thrombotic event by the SP-CUS did not lead to modification of the initial treatment. The initial treatment remained unchanged in 8 of the 12 patients (67%) in whom an asymptomatic venous thrombotic event was detected, all these patients continuing to receive anticoagulants. Of note, among the 12 asymptomatic venous thrombotic events diagnosed by the SP-CUS, only four involved extension to the deep venous system, all at a distal location, a situation for which there are no clear treatment guidelines. A positive SP-CUS may prompt a more aggressive therapy, even though no specific treatment has so far been validated in this situation.

By contrast, when no new venous thrombotic event was diagnosed by the SP-CUS, anticoagulant treatment was discontinued in 303 (71%) of the 429 patients initially treated with such drugs. The majority of the patients experiencing thromboembolic events during the follow-up had had their anticoagulant treatment prematurely discontinued after a negative SP-CUS. Therefore, it seems that the SP-CUS provided false reassurance to the physicians. Indeed, in the CALISTO study, no modification of treatment (placebo or fondaparinux at prophylactic dose) was planned on the basis of the intermediate evaluation in the absence of any clinical sign. Interestingly, the rate of symptomatic DVT at 77 days was 1.3% (0.7–1.9) in the placebo group, close to the incidence of symptomatic DVT at 3 months in this study (2.1% (0.8–3.3)). In our study, the SP-CUS evidently did not lead to an appropriate treatment modification in the sense that the overall outcome of the patients was no better than in the placebo group of the CALISTO study.[7]

Our results are in accordance with the absence of any recommendation in current guidelines[8] for an SP-CUS in patients presenting no new clinical signs.

In view of the cost of a CUS and the low rate of venous thromboembolic events, this form of therapeutic management does not seem to be cost effective.

This study is only descriptive. Ideally, to assess the relevance of performing an SP-CUS during the follow-up of patients with SVT, the use of this examination should have been randomised. Most of the patients included in the POST study received an anticoagulant treatment for their initial SVT, various treatment regimens being used. This precludes any conclusions concerning therapy. The very recent results of the CALISTO study[7] confirm that fondaparinux administered at prophylactic doses is effective and safe even in the absence of an SP-CUS. Thus, in the future, most patients with an isolated SVT will probably receive an anticoagulant treatment.

Conclusion

The use of an SP-CUS is neither efficient nor cost effective. Our results indicate the absence of any need for this examination.

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Conflict of Interest

Sara Quenet: none; Laurent Bertoletti: none; Jean-Pierre Laroche: none; Isabelle Quéré: none; Hervé Décousus: none; François Becker: none; Alain Leizorovicz: none.

Appendix

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