Individually tailored duration of elastic compression therapy in relation to incidence of the postthrombotic syndrome

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Objective: **We assessed whether individualized shortened duration of elastic compression stocking (ECS) therapy after acute deep venous thrombosis (DVT) is feasible without increasing the incidence of postthrombotic syndrome (PTS).**
Methods: **At the outpatient clinic of the Maastricht University Medical Centre, 125 consecutive patients with confirmed proximal DVT were followed for 2 years. Villalta scores were assessed on four consecutive visits; 3, 6, 12, and 24 months after the acute event. Reflux was assessed once by duplex testing. After 6 months, patients with scores ≤4 on the Villalta clinical score and in the absence of reflux were allowed to discontinue ECS therapy. If reflux was present, two consecutive scores ≤4 were needed to discontinue ECS therapy.**
Results: **ECS therapy was discontinued in 17% of patients at 6 months, in 48% at 12 months, and in 50% at 24 months. Reflux on duplex testing was present in 74/101 (73.3%) tested patients and was not associated with the onset of PTS. At the 6-month visit, the cumulative incidence of PTS was 13.3%, at 12 months 17.0%, and at 24 months 21.1%. Varicosities/venous insufficiency (present at baseline) was significantly associated with PTS; hazard ratio 3.2 (1.2-9.1).**
Conclusions: **Patients with a low probability for developing PTS can be identified as early as 6 months after the thrombotic event, and individualized shortened duration of ECS therapy based on Villalta clinical scores may be a safe management option. These findings need to be confirmed in a randomized clinical trial. (J Vasc Surg 2010;52:132-8.)**

Postthrombotic syndrome (PTS) is a chronic condition that arises in 20% to 50% of patients following deep venous thrombosis (DVT) and is therefore considered to be the most common complication of DVT.[1-4]

The quality of life is negatively affected by PTS, and substantial healthcare costs are generated.[5,6] Both the obstruction of limbs by residual thrombosis as well as the presence of reflux in the femoral vein and popliteal vein after an event of DVT are considered to be of importance for the development of valvular incompetence and of postthrombotic complaints.[7-10]

The diagnosis of PTS is usually made when both clinical symptoms indicative of PTS, as well as reflux, are present. Nevertheless, patients may have valvular incompetence after DVT but, at the same time, do not suffer from PTS.[11,12] The clinical diagnosis of PTS is based on clinical signs and symptoms that are scored according to a clinical scale.[13-15] Clinical manifestations of PTS are pain, edema, skin changes, venous claudication, and, in severe cases, even venous ulcers may occur. Elastic compression therapy has been observed to reduce the incidence of PTS in unselected patients by almost half.[16] The evidence supporting the value of compression therapy is derived from two randomized clinical studies only.[16-17]

These trials did not evaluate whether some patients could benefit more from long-term duration of compression therapy than others. Therefore, the issue whether all patients need to have compression therapy for a period of 2 years remains unclear. Compliance with therapy can be demanding for all patients, but possibly even more so for those patients who do not experience any complaints.

In a prospective management cohort study, we therefore assessed whether individualized duration of elastic compression therapy, after initial compression therapy of 6 months following an acute event of DVT, had an impact on the incidence of PTS. In addition, we evaluated whether some of the known risk factors for PTS can help select patients who can potentially benefit more from prolonged compression therapy.

METHODS

Patients

Consecutive patients with confirmed acute proximal DVT, defined as thrombosis in the popliteal vein (including the trifurcation), the femoral vein, or the common femoral vein, were followed for a period of 2 years after the acute event as part of routine patient care at the outpatient clinic of the Maastricht University Medical Centre, Maastricht, the Netherlands, between July 2003 and December 2006.

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All consecutive patients were considered for participation in the study; the only inclusion criterion was acute objectively confirmed proximal DVT, and there were no exclusion criteria.

Anticoagulant treatment was installed according to international guidelines and individually tailored when necessary.[18] Patients were provided with compression bandages within 24 hours of diagnosis, and no bed rest was prescribed. The initial treatment consisted of therapeutic doses of low molecular weight heparin (LMWH) for a period of at least 5 days, together with vitamin K antagonists. LMWH was stopped after reaching an international normalized ratio (INR) of two or higher on two consecutive measurements. Treatment was supervised by the Thrombosis Service Maastricht, an organization that closely monitors the INR of patients on anticoagulant treatment. Patients with provoked thrombosis were treated with anticoagulant medication for 3 months. In patients with a first event of idiopathic thrombosis, initial anticoagulant therapy was installed for a period of 6 months. All patients underwent compression ultrasound testing to assess residual thrombosis at 1 week before planned cessation of anticoagulant therapy. Whenever residual thrombosis was found at compression ultrasound examination, patients received extended anticoagulant therapy in order to reduce the risk of recurrent thrombosis.[19-21] Patients with previous events of venous thromboembolism were treated for at least 12 months or indefinitely.

Baseline examination

At the screening visit, a thorough medical check-up was performed, and a clinical history was taken. Risk factors were assessed both for venous thromboembolism (VTE) and for PTS. Risk factors for PTS included previous VTE, presence of malignant disease, obesity, age over 70 years, and history of varicose veins or venous insufficiency (signs and symptoms of venous insufficiency existing previous to the present acute event of DVT and/or previous treatment or operations for varicosities).

Elastic compression therapy

All patients were initially bandaged for as long as it took for the acute edema to resorb; new bandages were applied three times a week for a median duration of 4 weeks. Afterward, elastic compression stockings (ECS) were custom fitted, and patients were advised to wear these stockings during the daytime. The stockings prescribed were custom-made flat knitted stockings in two parts, one part for the upper section of the leg from thigh to knee; the other part was a knee-length stocking. A class III pressure was standard. For elderly patients and patients with arterial insufficiency, a class II stocking was stipulated (Mediven 550 [Medi Nederland BV, Breda, The Netherlands], ankle pressure 40 mm Hg [class III] or 30 mm Hg [class II]). All patients were advised to wear ECS for a minimal duration of 6 months after the acute event; the upper part of the stocking was worn for no longer than 6 weeks.

Assessments

Patients visited the outpatient clinic five times following the acute event in the context of regular patient care. The first visit took place within a month of the event, the second visit at 3 months after the event, the third at 6 months, the fourth at 12 months, and the final visit was at 24 months after the event.

The first visit (2-3 weeks after the event) was scheduled to assess the actual medical status (underlying malignancies, excess bleeding risk, and risk of recurrent thrombosis). A complete medical history was taken, and, in addition, a full physical examination was performed. No assessment of the affected leg was done at this first visit. Appraisal of patients in the subacute stadium was not performed because of the expected presence of complaints related to the acute phase of the event. The long-term effects of the thrombosis were assessed during the extended follow-up phase. All 125 patients were assessed at each of the four follow-up visits following the initial screening visit for compliance of elastic compression therapy. At each visit, a clinical assessment of the affected leg was performed, and signs and symptoms were scored using the Villalta score.[14] In addition, duplex ultrasound analysis was performed once (at 6 months after the event) during the entire follow-up period in all patients.

Compression ultrasound assessment for residual thrombosis. The initial diagnosis of DVT in the acute phase was based on the result of a compression ultrasound examination. Patients were re-examined 1 week before planned cessation of anticoagulant treatment. In case residual thrombosis was present, treatment was prolonged in order to diminish the risk of recurrence thrombosis.[19-21]

In all patients, results on re-examination were used as a reference for future assessments in case of new complaints.

Assessment for signs of the PTS. The presence of signs and symptoms indicative of PTS were scored according to the Villalta score.[14] This score contains five leg symptoms and six objective signs. The leg symptoms include pain, cramps, heaviness, pruritis, and paresthesia. The objective signs are pretibial edema, induration, new venous ectasia, redness, and pain during calf compression. For all items separately, a score of 0 to 3 could be assigned. Patients were classified as having PTS if they had a score of $\geq$5 or more on two or more consecutive visits that were at least 3 months apart. Venous ulceration was classified as severe PTS regardless of the sum score total.[14] The Villalta score was preferred over other existing scores because of its reported validity, sensitivity to change, and the relative simplicity of the assessment.[13,22] All patients were scored by one physician during the entire follow-up period. This physician was blinded to the results on duplex examination but not to the actual status of compression therapy.

Duplex ultrasound assessment for venous insufficiency. All patients underwent duplex ultrasound assessment in order to assess the presence of valvular insufficiency. Patients were examined in a reverse Trendelenburg position on a tilting table in a 45° angle, the knees flexed

and with the feet resting on a foot support. Ten vein segments were examined: the common femoral vein, the superficial femoral vein (proximal and middle), the long saphenous vein (proximal, middle, and distal), the popliteal vein, the short saphenous vein, and the posterior and anterior tibial veins. Reflux was measured in the longitudinal plane. Proximal reflux was measured after the Valsalva maneuver; distal reflux was measured by manual compression with sudden release. Normal duration of reflux in proximal veins was less than 1.0 seconds, in a distal vein less than 0.5 seconds. The scanner type used was Aloka SSD-2000 [Aloka Co Ltd, Tokyo, Japan]; the probe type used was a 7.5-MHZ linear transducer (for deep veins, a 3.5-MHZ transducer was used) at a low-flow setting.

Patient management

Patients were allowed to discontinue elastic compression after the initial 6 months of therapy based on absence of complaints (Villalta score ≤4) and absence of reflux on duplex ultrasound testing. In case a PTS score of ≥5 was present and/or if reflux was found, patients were advised to continue compression therapy. Patients with objectively confirmed reflux were allowed to stop compression therapy if PTS scores were ≤4 on two consecutive visits. Patients were diagnosed with PTS if they had a score of ≥5 on two separate occasions at least 3 months apart.

Statistical Analysis

A sample size of 125 patients was considered sufficient, based on the expected proportion of PTS in a population of 20% and the wish to exclude incidences up to 30% within a 95% confidence interval (CI), with a type I error of 0.05 and a type II error of 0.20.

Descriptive statistics were computed for baseline characteristics, and cross-tabulations were made for PTS scores per visit in relation to compression therapy.

Cumulative incidence of the PTS was estimated using the Kaplan-Meier method; 95% CIs were calculated using the standard error from the Kaplan-Meier estimation. Patients who were lost to follow-up or died were censored after their last visit.

The association between PTS and clinical characteristics was assessed for categorical variables using the Chi square test. The variables analyzed were risk factors for PTS, such as previous VTE, varicosities/venous insufficiency, obesity (cut-off body mass index, 26), age (cut-off, 70 years), gender, and duration of anticoagulant therapy, residual thrombosis, reflux, and malignancy.

Adjusted hazard ratios for the effect of compression therapy and their 95% CIs were calculated in the subsequent Cox regression analysis. All variables that generated a *P* value of ≤.05 in the univariate analysis were entered. All analyses were performed with SPSS software package 13.0 for Windows (SPSS, Inc, Chicago, Ill).

Table I. Baseline characteristics (N = 125)

Characteristics	*N (%)*
Men/women	51 (40.8)/74 (59.2)
Age in years	55.8 SD 1.48 (17-82)
Body mass index >26	65 (52)
Risk factors for VTE	
Recent trauma	26 (20.8)
Recent surgery	26 (20.8)
Malignancy	5 (4.0)
Hormonal therapy	26 (20.8)
Pregnancy/puerpurum	1 (0.8)
Known thrombophilia at presentation	7 (5.6)
Varicosities/venous insuffficiency	14 (11.2)
Travel >10 hours	8 (6.4)
Previous VTE	27 (21.6)
Previous DVT	18 (14.4)
Previous ipsilateral DVT	9 (7.2)
Treatment duration	
3 mo	25 (20)
6 mo	61 (48.8)
12 mo	16 (12.8)
24 mo or indefinite	21 (16.8)

DVT, Deep venous thrombosis; *VTE,* venous thromboembolism.

RESULTS

Patients

All 125 patients who visited the outpatient clinic for the follow up of an acute DVT were included in the analysis. The baseline characteristics for these patients are presented in Table I.

Clinical events. Of the 125 patients who were followed, complete follow-up was available for 102 patients. Twenty-one patients (16.8%) were lost to follow-up in the course of the 2-year follow-up period; two patients missed the visit at 6 months, two additional patients missed the 12-month visit, and 17 only missed the final visit. Of these 21 patients, six patients had moved away, three could not be followed due to substance abuse, three elderly patients had transportation difficulties, and one patient suffered a recurrent event and visited another hospital closer to her home, while, for the remaining eight patients, no particular reason for their lack of compliance could be identified.

Recurrence and death. Seven (5.6%) patients had an objectively documented recurrent event within the follow-up period. In addition, four (3.2%) patients died during the follow-up period (two male, two female; three of them died from metastasized malignancies (gastric, breast, lung), and there was one case of sudden death at home.

Use of ECS

Some patients with Villalta scores ≤4 stopped wearing compression stockings as early as 3 months (7 of 91 patients stopped on their own account); at 6 months 17% (16/94) did not wear stockings, at 12 months 52% (41/85), and at the 2-year follow-up visit 50% (41/82) did not have elastic compression anymore (Table II, Fig 1). The seven patients who stopped elastic compression on their own account developed no PTS. Of the patients who stopped compres-

Table II. Compression therapy during follow-up (N = 125)

Follow-up time	*Total N (%) compression*	*N (%) compression score ≥5*	*N (%) compression score ≤4*	*N (%) score unknown*
0-3 mo	118 (99.2%)	28/28 (100%)	84/91 (92%)	6*
4-6 mo	102 (86.4%)	24/24 (100%)	78/94 (83%)	7 (2†,2#,3*)
7-12 mo	58 (53.7%)	14/23 (61%)	44/85 (52%)	17 (3†,4#,10*)
13-24 mo	51 (53.1%)	10/14 (71%)	41/82 (50%)	29 (4†,21#,4*)

*No score.
†Death.
#Lost to follow-up.

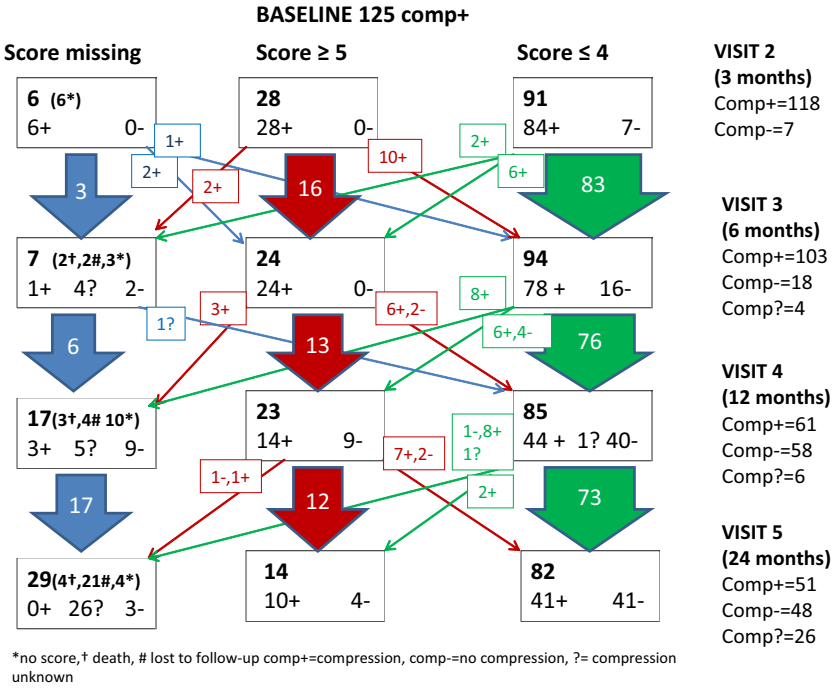

Fig 1. The patient flow during follow-up. The patients are grouped according to their Villalta score at each particular visit (3 months, 6 months, 12 months, and 24 months). The bold arrows depict the patient group who remains within their original score (around 50% for those with a score ≥5 and around 85% for those with a score of ≤4). The small arrows represent patients who have variable scores in between visits. The numbers in the squares indicate patients with ECS (+) and patients without ECS (−), and, in cases where it is unknown whether the patient had ECS, (?). In some cases, the Villalta score is missing (*), the patient died (†), or is lost to follow-up (#).

sion therapy based on a low clinical score, five patients restarted compression therapy because of worsening of symptoms. These patients, although they did discontinue compression therapy for quite some time, did not develop PTS. Patients with Villalta scores ≥5 were all wearing stockings for at least 6 months. Although not advised to discontinue compression therapy, almost 40% (9/23) of patients stopped wearing ECS. At 1 year, 60.9% (14/23) were compliant with compression therapy; at the 2-year follow-up visit, the compliance with therapy increased to 71.4% (10/14; Table II, Fig 1).

Duplex ultrasound testing

Duplex ultrasound testing for reflux was done in 101 (80.8%) patients; a total of 74 (73.3%) had reflux either in the superficial veins or in the deep venous system or both. Thirty-one (31%) patients in whom reflux was objectively confirmed in the deep vein system had repeated duplex testing; no improvement was seen on repeated duplex ultrasound testing over time. Of the 74 patients with reflux, 40 stopped wearing ECS in the course of the follow-up. Thirty-one (77.5%) patients had a low PTS score, and nine (22.5%) patients had a high PTS score.

Postthrombotic complaints and syndrome

Approximately 75% of all patients had a stable low score (≤4), and approximately 15% had a stable high score (≥5). Patients with severe PTS could already be identified at the 6-month visit (Table III, Fig 1). Only a very small proportion of patients (2%) worsened after 1 year. Overall, 37

Table III. Villalta-Prandoni scores during follow-up (N = 125)

Follow-up time	*Score missing*	*>5-14*	*>15*
3 mo	5 (4%)	25 (20%)	3 (2.4%)
6 mo	4 (3.2%)	23 (18.4%)	2 (1.6%)
12 mo	22 (17.6%)	22 (17.6%)	2 (1.6%)
24 mo	29 (23.2%)	13 (10.4%)	2 (1.6%)
Any time	38 (30.4%)	37 (29.6%)	3 (2.4%)

Table IV. Cumulative incidence of PTS during follow-up (Kaplan-Meier estimates)

Follow-up time	*Number at risk*	*N (95% CI) total PTS (cum)*	*N (95% CI) Severe PTS (cum)*
3 mo	125	0 (–)	0 (–)
6 mo	125	16 (13.3 ± 6.08)	2 (1.65% ± 2.27)
12 mo	94	20 (17.0 ± 6.80)	3 (2.56% ± 2.86)
24 mo	79	24 (21.1 ± 7.59)	3 (2.56% ± 2.86)

CI, Confidence interval; *PTS,* postthrombotic syndrome.

(29.6%) patients had a Villalta score of ≥5 on any of the four visits. Based on the definition of the PTS, a score of ≥5 on two separate occasions at least 3 months apart, only 24 (21.1%) of the 125 patients developed the syndrome in the course of the 2-year follow-up period. Three of these patients had severe PTS, one of whom was diagnosed with and treated for a venous ulcer at another hospital (Table III).

It is interesting to note that many patients with initial scores above the threshold of 5 have lower scores at later visits. Of the 29 patients that are not included in the final assessment (21 who were lost to follow-up and eight who had no Villalta score available for the last assessment), seven (24 %) had a high score at the last available assessment, and 20 (69%) had a low score at the last available assessment; for two (7%), no scores were available.

At 6 months after the event, 16 patients met the criteria for the diagnosis of PTS. At 12 months, an additional four patients were newly diagnosed with the syndrome, resulting in 20 symptomatic patients. After 24 months, a further four patients developed PTS, leading to a total of 24 patients with symptomatic PTS at visit five. At 6 months, the cumulative incidence of PTS was 13.3% (95% CI, 7.2-19.4), at 12 months 17.0% (95% CI, 10.2-23.8), and at the 24-month visit 21.1% (95% CI, 13.5-28.7) (Table IV).

Risk factors for the PTS

Of the tested variables, only reflux, varicosities/venous insufficiency, and anticoagulant therapy with a duration of 3 months were significantly associated with PTS in the univariate analysis. Duration of anticoagulant treatment of 3 months was negatively associated with PTS (odds ratio [OR], 0.13; 95% CI, 0.02-0.84; $P = .04$). We found that these patients more often lacked residual thrombosis: 17.4% vs 39.4% (OR, 0.32; 95% CI, 0.11-0.99; $P = .05$). A positive association with PTS was observed for varicosities/venous insufficiency (OR, 7.5; 95% CI, 2.3-24.5; $P \leq .001$) and for combined reflux on duplex ultrasound (OR, 7.5; 95% CI, 1.19-45.8; $P = .04$); deep reflux alone was not significantly associated with the outcome.

In the subsequent Cox regression analysis, however, only the association with varicosities/venous insufficiency remained significant (adjusted HR 3.2; 95% CI, 1.2-9.1; $P = .028$). Previous episodes of VTE, age, gender, residual thrombosis, and longer duration of anticoagulant therapy, malignancy, reflux, and obesity were not associated with PTS.

Within the group of patients with varicosities/venous insufficiency, 36% (5/14) had previously experienced thrombosis compared with 19.8% (22/111) in the group of patients with no previous episodes of DVT; this difference, however, was not significant.

DISCUSSION

We found that tailoring the duration of elastic compression therapy based on the Villalta clinical score did not have a negative impact on the subsequent incidence of PTS. The outcome of our study showed that individualized duration of compression therapy results in a cumulative incidence of PTS over a 2-year period of 21.1% with a 95% CI of 13.5 to 28.7. This compares well with results of active arms in randomized studies.[16,17] Similar results were found in a recently published randomized but underpowered trial. The incidence of PTS assessed according to the CEAP classification was low in both the group that stopped at 6 months (20%) as well as in the group that continued compression therapy for 24 months (13.1%).[23]

In our study, all patients were advised to wear ECS for at least 6 months. The rationale for this was based both on literature and on practical considerations. Literature suggests that thrombus regression takes at least 6 months and can benefit from compression therapy.[7,24-27] Moreover, the appraisal of patients in the subacute stadium of DVT is difficult because of complaints related to the acute phase of the thrombosis; it is therefore more desirable to assess patients at a later moment in time.[12]

The presence of reflux as well as residual thrombosis is believed to be important for venous hypertension, but no consistent significant association with PTS with any of these two factors has been found in our patient population, nor have these associations been established previously by others.[8,12] Although valvular reflux was found in approximately 70% of all patients, this did not significantly contribute to the outcome of PTS. Even in the presence of valvular reflux, low scores on the Villalta score were common, and discontinuation of elastic compression therapy in these patients did not result in the development of PTS. We feel, therefore, that this lack of association with the outcome of PTS justifies the abolition of duplex reflux testing in future assessment of patients for the individualization of elastic compression therapy. Within the group of patients with PTS, however, duplex testing will still retain its merits for assessment of venous outflow resistance and diagnostic work-up for surgical interventions.[28-30]

In our cohort, a strong association with PTS was found for varicosities/venous insufficiency. Although part of our patients with varicosities/venous insufficiency experienced an earlier event, the percentage of previous events differed not significantly from patients without varicosities/venous insufficiency and is therefore not likely to explain the association to the outcome of PTS.

In the follow-up, four out of nine patients who had previous thrombosis in the ipsilateral leg were eventually diagnosed with PTS. This number of patients, however, was not large enough to allow for definitive conclusions; no significance was reached due to the small sample size. The observation that 45% of patients with ipsilateral recurrence developed PTS is in line with previous published findings by other authors.[16,31]

Overall, we only identified a small group of patients with a strong predisposition for PTS; they developed PTS regardless of adequate elastic compression therapy. For the small group of patients who develop PTS, more effective treatment options should therefore be established.[29,30,32-34]

Some weaknesses of our study have to be addressed. First, our study was not a randomized trial but rather a prospective management cohort study. The study had an open character and was, as a result, prone to bias. Therefore, in order to be able to draw firm conclusions on the subject of individual tailoring of elastic compression therapy, it would be desirable to perform an adequately powered, randomized clinical trial. Secondly, some known strong predictors, such as recurrent thrombosis in the ipsilateral leg, could not be confirmed because we did not have a sufficient number of patients with previous ipsilateral thrombosis of the leg in our study. A strong point of our study is the inclusion of all consecutive patients with proximal DVT and, therefore, the generalizability of the applied management strategy.

In conclusion, our data suggest that after an acute event of DVT, elastic compression therapy can be tailored individually without an adverse effect on PTS incidence. Selection of patients for a shorter duration of elastic compression therapy can be based on clinical scores only. A randomized clinical trial is needed to confirm these data.

AUTHOR CONTRIBUTIONS

Conception and design: AC, MP, HC
Analysis and interpretation: AC, MP
Data collection: AC
Writing the article: AC, MP, KH, JT, HC
Critical revision of the article: AC, MP
Final approval of the article: AC, MP, KH, JT, HC
Statistical analysis: AC, MH
Obtained funding: N/A
Overall responsibility: AC

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