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The IDEAL DVT study, individualized duration elastic compression therapy against long-term duration of therapy for the prevention of post thrombotic syndrome, a randomized controlled trial

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3 Study Protocol

4 The IDEAL DVT study, individualized duration elastic compression therapy against long-term duration
5 of therapy for the prevention of post thrombotic syndrome, a randomized controlled trial
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50 protocol, RCT
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Abstract**Introduction:**

Post thrombotic syndrome (PTS) is a serious complication of deep vein thrombosis (DVT) of the leg that affects 20-50% of patients. Once a patient experiences PTS there is no treatment that effectively reduces the debilitating complaints. Two randomized controlled trials showed that elastic compression stocking (ECS) therapy after DVT for 24 months can reduce the incidence of PTS by 50%. However, it is unclear whether all patients benefit to the same extent from ECS therapy or what the optimal duration of therapy for individual patients should be. ECS therapy is costly, inconvenient, demanding and sometimes even debilitating. Tailoring therapy to individual needs could save substantial costs. The objective of the IDEAL DVT study therefore is to evaluate whether tailoring the duration of ECS therapy on signs and symptoms of the individual patient is a safe and effective method to prevent PTS, compared to standard ECS therapy.

Methods and analysis:

A multicentre, single-blinded, allocation concealed, randomized, non-inferiority trial. A total of 864 consecutive patients with acute objectively documented proximal DVT of the leg are randomized to either standard duration of 24 months or tailored duration of ECS therapy following an initial therapeutic period of 6 months. Signs and symptoms of PTS are recorded at regular clinic visits. Furthermore, quality of life, costs, patient preferences and compliance are measured. The primary outcome is the proportion of patients with PTS after 24 months.

Ethics and dissemination:

Based on current knowledge the broad application of ECS therapy is questioned. The IDEAL DVT study will address the central questions that remain unanswered: What individual patients do benefit from ECS therapy and what is the optimal individual treatment duration? Primary ethics approval was received from the Maastricht University Medical Centre.

Results of the study will be disseminated via peer-reviewed publications and presentations at scientific conferences.

Trial Registration:

NCT01429714 and NTR 2597

Background

After deep vein thrombosis (DVT) 20-50% of patients develop post thrombotic syndrome (PTS). PTS is a chronic condition, characterized by leg complaints such as pain; heaviness; cramps; aching; tingling; and leg signs due to venous insufficiency, evolving in severe cases to venous ulceration of the leg that was affected by the DVT.¹⁻⁴ PTS is a serious affliction, with substantial impact on quality of life and costs.¹⁵ Because an effective therapy is lacking, prevention of PTS is of major importance. Up till now, elastic compression stocking (ECS) therapy after DVT is the mainstay of PTS prevention. The evidence sustaining the value of ECS therapy following acute DVT is derived from 2 randomized clinical trials.⁶⁷ Incidences of PTS were reduced significantly (approximately 50%) by application of ECS therapy for 24 months in all patients in these studies. However, based on these trials it is still undecided whether all patients benefit to the same extent from ECS therapy or what the optimal duration of ECS therapy for individual patients should be. There have been other studies that highlighted different aspects of ECS therapy. A significant benefit of early ambulation and early compression measured as mean score on Villalta (a score containing 5 leg symptoms and 6 objective signs), was found in a follow-up study of a small trial that compared ambulation combined with inelastic compression (Unna boot) or ECS therapy to bed rest without any compression in the acute phase of 9 days, followed by ECS therapy for all patients during 2 years of follow up.⁸⁹ ECS therapy may not be indicated for all patients as shown by a study that assessed whether ECS therapy initiated one year after the event of DVT would lower the incidence of PTS in patients without complaints but with reflux on duplex testing. No significant benefit of ECS therapy at this late time of onset was found. The incidence of PTS was low in both groups.¹⁰ Only one study so far assessed whether prolonged duration of ECS therapy was superior to 6 months of ECS therapy following an event of proximal DVT. In this study no significant difference in the incidence of PTS according to the CEAP classification was observed between the two treatment groups.¹¹ The safety of shortened duration of ECS therapy based on individual patient clinical scores was assessed in our management study, and we showed that tailoring the duration of ECS therapy based on the signs and symptoms of the individual patient after an initial treatment period of 6 months, is a safe strategy to prevent PTS.¹² We found that 50% of our patients did not need ECS therapy for as long as 2 years, while the overall incidence of PTS was 21.1% (95% CI 13.5- 28.7). This is comparable to published incidences after 24 months ECS therapy.⁶

⁷ In the Netherlands, each year around 25.000 patients experience a new event of DVT. In order to

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2 prevent PTS, common practice is to prescribe custom fitted ECS therapy for 2 years for all patients.¹³

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14 ECS therapy is costly, demanding and sometimes even debilitating. Elderly patients can often not apply the ECS by themselves but need help from family or they even need home care visits (7.5%).¹⁵⁻

17 Total annual costs of ECS therapy roughly amounts to 2.5 million for stockings (25.000 patients*100 euro) and 21 million for home care (7.5%*25.000 patients*500 visits*20 euro).¹⁵⁻¹⁷ Moreover, the majority of patients do not experience any post thrombotic complaints.¹⁰ In the Netherlands, over 10 million euro each year could be saved if ECS treatment would be individualized. The results of a recently published trial performed by Kahn et al. refuted the routine wearing of ECS after DVT altogether. This study showed no treatment effect at all from ECS therapy in contrast to the large treatment effects found in previous non-placebo controlled trials.^{6 7} The unexpected lack of effectiveness cannot be dismissed solely as a placebo effect. The compliance to ECS therapy, a major determinant of effectiveness, was 55.6% after 24 months, less than in the previous trials by Brandjes and Prandoni et al, where compliance was considerably higher, up to 90%.^{6 7 18} Because compliance to therapy is one of the most important features for successful ECS therapy, we will perform a discrete choice experiment in which patient preferences towards ECS therapy will be assessed and the main obstacles for compliance to therapy will be addressed.

Based on current knowledge it is understood that the broad application of ECS therapy is questioned. Especially the benefit to individual patients and the optimal duration of ECS therapy were never studied properly and as a result it is unclear which individual patients require therapy and for how long.

The IDEAL DVT study aims to address these topics. In addition quality of life, patient preference towards ECS therapy, compliance tot therapy, as well as cost-effectiveness of ECS therapy will be assessed. The primary outcome is the proportion of patients with PTS at the end of follow-up.

Methods/Design

A multicentre, single-blinded, allocation concealed, randomized, non-inferiority trial comparing individually tailored duration of ECS therapy (intervention) with standard duration of 24 months ECS therapy (control), for the prevention of PTS. Randomization will guarantee a fair distribution of patients within each patient group. Stratification will be performed on centre and potentially confounding effects such as age, sex and body mass index. The study will be a multi center study in order to get a good

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3 representation of patients and to achieve sufficient patient numbers. The primary outcome will be PTS
4 at 24 months after the event; the observers will be blinded to the allocated treatment arm. The
5 allocation will be concealed from study personnel involved in assessing the leg symptoms and rating
6 the PTS scores. Both randomization and allocation concealment are used as strategies against bias.
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8 The study is not double blinded; no inactive stockings will be used in the comparator group. The use of
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10 sham stockings will very likely interfere with the quality of life and will complicate the assessment of
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12 perceived differences between groups. Patients will be followed for the entire study duration; incidence
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14 of recurrent DVT and VTE related death during the follow-up period will be documented.
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20 Patients and treatment

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22 Consecutive, consenting adults with an acute objectively documented proximal DVT of the leg,
23 adequately treated with anticoagulant treatment are included in the study. Patients are included within
24 6 weeks after DVT. Exclusion criteria are: previous DVT in the affected leg, recurrent DVT in the 6
25 months following inclusion, pre-existent venous insufficiency (skin signs C3-C6 on CEAP score or
26 requiring ECS therapy), contraindication for ECS therapy such as intermittent claudication or clinical
27 signs of leg ischemia or asymptomatic arterial insufficiency (a pulse deficit or bruit at sites of narrowing
28 at physical examination), active thrombolysis, and limited life expectancy (< 6 months).
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35 Patients are recruited from 12 hospitals in the Netherlands and 2 hospitals in Italy. In the initial acute
36 phase after DVT, until the acute oedema has disappeared, three strategies will be applied. The leg is
37 either bandaged with short stretch bandages to a compression of 30-40 mmHg, worn day and night
38 and redressed twice per week; or a bandage stocking with 35mmHg compression is prescribed
39 (Mediven Struva 35[®], Medi, Breda, the Netherlands), worn day and night; or no initial compression
40 therapy is applied, according to the strategy of the hospital protocol. After the initial phase, a custom
41 fitted, flat knitted, knee length graduated elastic compression stocking class III (ankle pressure 40
42 mmHg) is prescribed for all patients. Patients are advised to wear the stockings during the daytime.
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51 Procedures

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53 After obtaining written informed consent, randomization is performed centrally at the coordinating
54 study centre, the Maastricht University Medical centre. Patients are randomized to one of the two
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3 treatment arms. (Figure 1) A web-based randomisation program (TENALEA (Trans European Network
4 for Clinical Trials Services)) is used that executes blocked randomisation with stratification on centre-
5 level and on possible confounding patient characteristics such as age, sex, and Body Mass Index.
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7 Permutated blocks of randomly varying size are used to maintain balance of numbers in each treatment
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9 group and to ensure allocation concealment.

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11 Information on allocation is only accessible to the study personnel at the coordinating study centre in
12 Maastricht, and patients will receive information about their allocation via the coordinating study
13 centre. The allocation will be concealed from study personnel involved in assessing the leg symptoms
14 and rating the PTS scores. Patients are not blinded by the use of sham stockings, because they may
15 influence quality of life, complicating the assessment of perceived differences between groups.
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17 Patients are asked not to reveal their treatment allocation to their own physician, and not to wear the
18 elastic compression stocking at the day of their outpatient clinic visits.
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27 All patients are advised to wear the elastic compression stocking during the first 6 months after DVT.
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29 In the control group, all patients are instructed to wear the elastic compression stocking daily for a total
30 duration of 2 years. In the Intervention group, duration of ECS therapy is individually tailored based on
31 Villalta scores.¹⁹ After the first 6 months therefore, there are three scenarios:

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34 (1) The Villalta score at both the 3 and 6-month follow-up visit is ≤ 4 . Then the patient is advised
35 to discontinue ECS therapy.
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37 (2) The Villalta score at the 3-month follow-up visit is ≥ 5 the Villalta score at the 6 month follow-
38 up visit is ≤ 4 . The patient is advised to continue the ECS therapy for another 6 months. If the
39 Villalta score at the 12 month follow-up visit is ≤ 4 , the patient is allowed to discontinue the
40 ECS therapy,
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42 (3) The Villalta score is ≥ 5 at both the 3 and 6 months follow-up visit. The patient is advised to
43 continue the ECS therapy for a total duration of 24 months. (Figure 2)
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51 Once stopped, ECS treatment will not be reinstated. Using this algorithm the duration of ECS therapy
52 is individually tailored in each patient. The decision on the duration of ECS therapy in patients in the
53 intervention group is made centrally at the coordinating study centre, as only there the information on
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3 treatment allocation is available. The patient is informed about the decisions on the (dis) continuation
4 of the ECS therapy by the coordinating centre.
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8 Follow-up 9

10 All patients are followed for 24 months after DVT. During these 24 months they visit the outpatient
11 clinic 4 times: at 3, 6, 12, and 24 months after the DVT. At each follow-up visit the signs of PTS will be
12 recorded and scored, by the study nurse or the treating physician, using the objective part of the
13 Villalta clinical scale for PTS.¹⁹ In case of intermittent leg complaints or signs or symptoms suspect of
14 recurrent VTE, patients are instructed to visit their treating physician. Study documentation will be
15 filled out and adverse events will be recorded. The CCMO (central committee human related research)
16 will be notified in case of serious adverse events or death.
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24 The patient is asked to fill out 5 questionnaires: at baseline, and 3, 6, 12 and 24 months later. All
25 questionnaires will be offered as a web based application, each patient will have a unique personal
26 entry code. For patients who are not able or willing to use the electronic questionnaires, a paper
27 version will be available. The first questionnaire is filled out shortly after inclusion (4-6 weeks after
28 DVT) and the subsequent questionnaires are filled out the day before each follow-up visit. All
29 questionnaires contain the subjective part of the Villalta clinical scale for PTS¹⁹⁻²³, questions on ECS
30 compliance, a cost questionnaire, and three health related quality of life (HRQOL) questionnaires: the
31 Dutch translated Veines-Qol²³, the SF-36²⁰, and the EuroQOL-5D²¹. In a subset of the study
32 population patient preferences regarding elastic compression therapy will be analysed, by conducting
33 a discrete choice experiment (DCE). For this purpose, a DCE questionnaire will be send to a subset of
34 the population at approximately 3 months after DVT.
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45 Compliance to ECS therapy is monitored in two ways. Each questionnaire contains a question on
46 compliance to the advised version of ECS therapy. Because compliance and adherence to therapy is
47 of crucial importance the number of contact moments for the assessment of compliance with ECS
48 therapy will be increased by adding telephone contacts to the regular clinical visits. Study-supporting
49 staff will make computer-assisted random telephone calls during the entire follow-up period to both the
50 patients in the group with the 2-year ECS intervention and to patients in the group with individualized
51 ECS therapy. The telephone calls will be made randomly to create a surprise effect (patients are off
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3 guard) and to allow for a distribution of contacts over the entire study period. Per patient 3 extra
4 contact moments will be created. A standard questionnaire will be used to assess compliance and to
5 address reasons for non-compliance. Crossover to another therapy arm will be discussed and
6 discouraged.
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16 The primary outcome is the proportion of patients with PTS at the end of follow-up, 24 months after
17 DVT. PTS is defined as a Villalta score of ≥ 5 at two consecutive visits that are at least three months
18 apart. Although the consensus is to diagnose PTS at the 6-month visit or later based on one single
19 Villalta score ≥ 5 ²⁴, we modelled this study after the preceding management study in which two
20 consecutive Villalta scores ≥ 5 were needed for the diagnosis PTS. We observed that a proportion of
21 patients (about 12%) had fluctuating Villalta scores beyond 6 months after the acute event of DVT.
22 Assigning the diagnosis based on one single score ≥ 5 would therefore lead to misclassification and
23 overestimation of the PTS incidence. The Villalta scores at 6 months will be available; therefore also
24 the proportion of patients with PTS according to the consensus scoring method will be presented.
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36 Secondary outcomes include:

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38 1. HRQOL, measured by questionnaires (SF-36²⁰, EuroQOL-5D²¹, Dutch translated Veines-QoL²³, 2.
39 Costs²², 3. Recurrent thrombosis, according to criteria as published²⁵ and assessed by objective
40 tests, 4. VTE related death during follow-up, assessed by an independent and blinded adjudication
41 committee, 5. Patient preferences, assessed with a Discrete Choice Experiment (DCE)²⁶.
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49 Since both effects on costs and generic health-related quality of life are to be expected, the method of
50 economic evaluation is a cost-utility analysis (CUA). The analysis will be from a societal perspective.
51 The primary effect parameter is generic health-related quality of life, measured in quality adjusted life
52 years (QALYs). We will perform two analyses: a trial based CUA with a time horizon of two years
53 (identical to the duration of follow up in the clinical study), and a model-based CUA with a lifelong time
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3 horizon. For the latter, we will follow the guidelines of good modelling.²⁷ We will be able to adapt a
4 Markov model for diagnostic strategies in DVT, which was developed by our group earlier.²⁸ Costs in
5 the economic analyses include direct health care costs (medical costs for prevention, diagnostics,
6 therapy, rehabilitation and care), direct non-health care costs (travel costs) and indirect costs
7 (productivity loss). Utilities will be calculated from the responses on the EQ-5D and SF36 classification
8 systems using the available multi-attribute utility functions.^{29 30}

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14 The results of the DCE will provide insight in the trade-offs patients make between characteristics of
15 the therapy. More specifically, we will investigate what duration of ECS therapy, with its drawbacks,
16 patients consider to be acceptable.
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20 21 Sample size calculation

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23 The proposed study is a non-inferiority trial and aims to demonstrate that the assessed alternative
24 therapy based on ECS for 6 months followed by individually prolonged ECS therapy based on Villalta
25 scores is not worse than the comparator ECS therapy for a standard duration of 24 months, by more
26 than the prespecified amount of 7.5% (the non-inferiority margin). The published incidence of PTS
27 following two years of ECS lies between 20 and 30%. (Prandoni 24.5% (95% CI 15.6- 33.4), Brandjes
28 20% (95% CI 12.4-29.2) As it is statistically impossible to demonstrate equivalence (prove the H0 of
29 no difference), Blackwelder proposed a one sided significance test to reject the null hypothesis by a
30 clinically acceptable amount.³¹ If we allow a difference of 7.5% in the outcome PTS between the group
31 with ECS for 2 years and the group with the alternative therapy, 70% of the effect will be preserved.
32 This proportion of loss in efficacy is customarily accepted in controlled randomized clinical trials. At a
33 one sided significance level of 0.05 and a power of 80%, with a ratio of 1, a total of 847 patients is
34 needed to provide sufficient patients for an adequately powered trial.^{31 32} Loss to follow-up of patients
35 is expected to be less than 2% since the intervention does not have an invasive nature. Therefore, a
36 total of 864 patients are needed (432 patients per treatment arm).
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50 51 Statistical analysis

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53 Descriptive statistics of the total population and of the two treatment groups separately will be
54 computed to provide baseline characteristics of the patients in both treatment arms.
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3 For the primary outcome PTS, univariate analysis of all proportions will be performed with logistic
4 regression (chi-squared) analysis. Kaplan-Meier method will be used to calculate the cumulative
5 incidences of PTS, adjusted for centre, to compare incidence rates between the two treatment arms.
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7 Patients who die or are lost to follow-up will be censored at their last visit. ANOVA will be applied to
8 assess the changes over time for different outcome measures.
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10 Hazard ratio's and 95% confidence intervals for both treatment arms will be calculated using Cox
11 regression models. Hazard ratio's will be adjusted for age, sex, clinical presentation of DVT, and
12 extent of the index deep vein thrombosis.
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20 Interim analysis (safety)

21 A prespecified safety analysis will be performed when 50% of the subjects have completed the 2-year
22 follow-up. The analysis will be performed by the coordinating centre, and supervised by the principal
23 investigators. The safety analysis will be performed to assess significant enhanced risk of PTS or
24 excess morbidity/mortality in the intervention arm of the study population. Fisher's exact test will be
25 performed to compare incidence of PTS at a significance level of 0.05 (two sided). The study can
26 be stopped in case of significant excess morbidity/mortality in the alternative treatment arm.
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34 Ethical considerations

35 The medical ethical committee of the Maastricht University Medical centre approved this study. All
36 patients are extensively informed about the study, and written informed consent is obtained from all
37 participating patients.
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43 Discussion

44 Based on current knowledge the broad application of ECS therapy after DVT is questioned. The
45 results of a recently published trial performed by Kahn et al. refuted the routine wearing of ECS after
46 DVT altogether (ref). This study showed no treatment effect at all from ECS therapy (graduated ECS
47 30-40 mmHg) compared to placebo ECS therapy (5 mmHg). This is in sharp contrast to the large
48 treatment effects found in previous non-placebo controlled trials.⁶⁷ The unexpected lack of
49 effectiveness cannot be dismissed solely as a placebo effect. The compliance to ECS therapy, a major
50 determinant of effectiveness, was 55.6% after 24 months, much less than in the previous trials by
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3 Brandjes and Prandoni et al, where compliance was considerably higher, up to 90%.^{67 18} Therefore
4 the definitive answer on the usefulness of ECS therapy for the prevention of PTS is not yet provided.
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6 The need for the IDEAL DVT remains unchanged. The benefit to individual patients and the optimal
7 duration of ECS therapy were never studied properly and as a result it is unclear which individual
8 patients require therapy and for how long. The IDEAL DVT study will address the central questions
9 that remain unanswered: What individual patients do benefit from ECS therapy and what is the
10 optimal individual treatment duration? The study that we plan to perform is not only innovative; for the
11 first time individual tailoring of duration of ECS therapy will be investigated, but also it will provide
12 unique additional knowledge on the safety, effectiveness and cost- effectiveness of this approach. The
13 IDEAL DVT study started including patients March 2011 and is currently on-going.
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Trial status

The IDEAL DVT study is currently in progress. Patient recruitment started March 15th 2011 and is still on-going.

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We especially acknowledge the participating investigators.

Competing interests

The authors declare that they have no competing interests.

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Contributions

AtC wrote the protocol and designed the study, the other authors MJ (cost-effectiveness research), MP (study design/statistics) and HtC (study design) contributed. AB is a PhD student and coordinator of the trial.

Ethics approval

Maastricht University Medical Centre.

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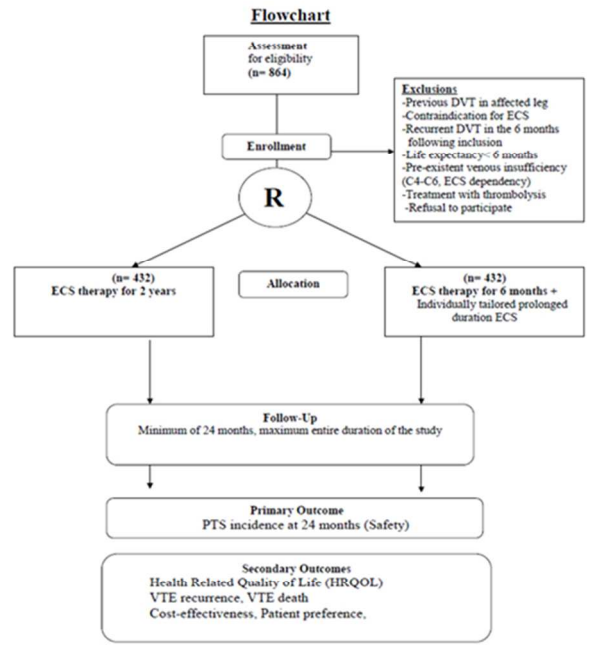
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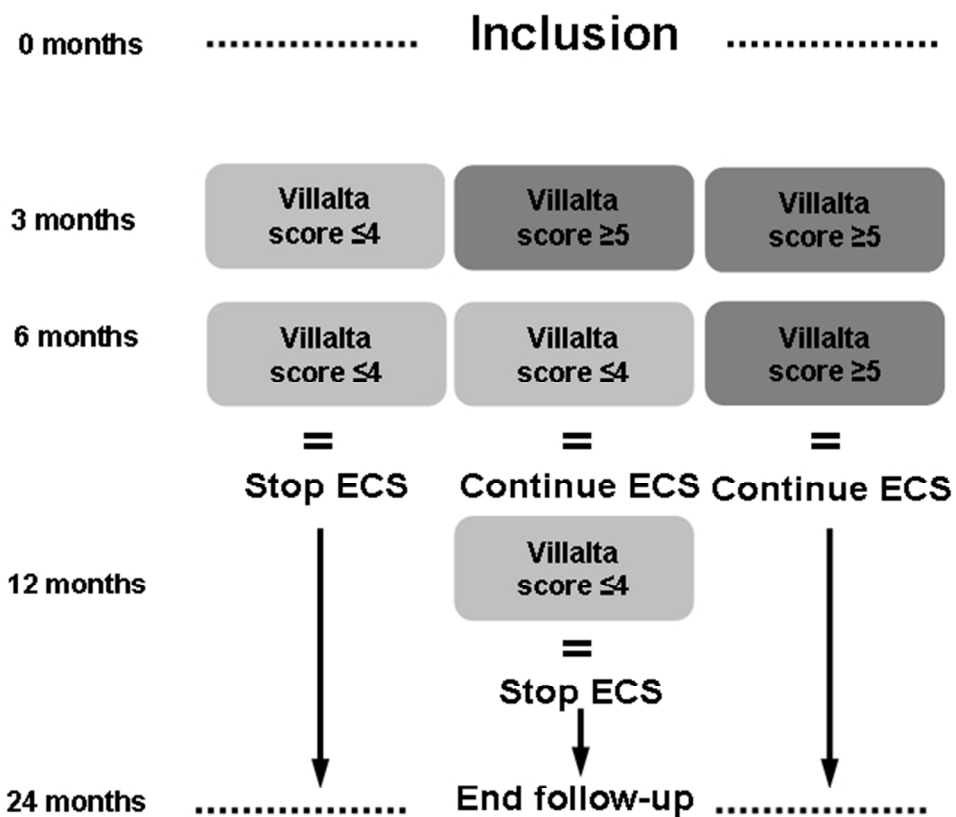
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Study flow diagram
254x190mm (96 x 96 DPI)

Review only



Algorithm individually tailored ECS therapy
177x161mm (96 x 96 DPI)

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BMJ Open

The IDEAL DVT study, individualized duration elastic compression therapy against long-term duration of therapy for the prevention of post thrombotic syndrome, a randomized controlled trial

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Manuscripts

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3 Study Protocol

4 The IDEAL DVT study, individualized duration elastic compression therapy against long-term duration
5 of therapy for the prevention of post thrombotic syndrome, a randomized controlled trial
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49 Key words: Post thrombotic syndrome, deep vein thrombosis, elastic compression stocking therapy,
50 protocol, RCT
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52 Word count: 3345
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Abstract**Introduction:**

Post thrombotic syndrome (PTS) is a serious complication of deep vein thrombosis (DVT) of the leg that affects 20-50% of patients. Once a patient experiences PTS there is no treatment that effectively reduces the debilitating complaints. Two randomized controlled trials showed that elastic compression stocking (ECS) therapy after DVT for 24 months can reduce the incidence of PTS by 50%. However, it is unclear whether all patients benefit to the same extent from ECS therapy or what the optimal duration of therapy for individual patients should be. ECS therapy is costly, inconvenient, demanding and sometimes even debilitating. Tailoring therapy to individual needs could save substantial costs. The objective of the IDEAL DVT study therefore is to evaluate whether tailoring the duration of ECS therapy on signs and symptoms of the individual patient is a safe and effective method to prevent PTS, compared to standard ECS therapy.

Methods and analysis:

A multicentre, single-blinded, allocation concealed, randomized, non-inferiority trial. A total of 864 consecutive patients with acute objectively documented proximal DVT of the leg are randomized to either standard duration of 24 months or tailored duration of ECS therapy following an initial therapeutic period of 6 months. Signs and symptoms of PTS are recorded at regular clinic visits. Furthermore, quality of life, costs, patient preferences and compliance are measured. The primary outcome is the proportion of patients with PTS at 24 months.

Ethics and dissemination:

Based on current knowledge the standard application of ECS therapy is questioned. The IDEAL DVT study will address the central questions that remain unanswered: What individual patients do benefit from ECS therapy and what is the optimal individual treatment duration? Primary ethics approval was received from the Maastricht University Medical Centre.

Results of the study will be disseminated via peer-reviewed publications and presentations at scientific conferences.

Trial Registration:

NCT01429714 and NTR 2597

Background

After deep vein thrombosis (DVT) 20-50% of patients develop post thrombotic syndrome (PTS). PTS is a chronic condition, characterized by leg complaints such as pain; heaviness; cramps; aching; tingling; and leg signs due to venous insufficiency, evolving in severe cases to venous ulceration of the leg that was affected by the DVT.¹⁻⁵ PTS is a serious affliction, with substantial impact on quality of life and costs.^{2,6} Because an effective therapy is lacking, prevention of PTS is of major importance. Up till now, elastic compression stocking (ECS) therapy after DVT has been the mainstay of PTS prevention. The evidence sustaining the value of ECS therapy following acute DVT is derived from 2 randomized clinical trials, which showed that incidences of PTS were reduced by approximately 50%, with application of ECS therapy for 24 months.^{7,8} However, based on these trials it is still undecided whether all patients benefit to the same extent from ECS therapy or what the optimal duration of ECS therapy for individual patients should be. We have previously assessed the safety of shortened duration of ECS therapy based on individual patient clinical scores in a management study of 125 patients, and we have shown that tailoring the duration of ECS therapy based on the signs and symptoms of the individual patient after an initial treatment period of 6 months, is a safe strategy to prevent PTS. We found that 50% of our patients did not need ECS therapy for as long as 2 years, while the overall incidence of PTS was 21.1% (95% CI 13.5- 28.7).⁹ This incidence is comparable to published incidences after 24 months ECS therapy.^{7,8} While this was a prospective management cohort study with an open character and therefore prone to bias, the results of this study need to be confirmed by an adequately powered randomized controlled trial. There have been other studies that highlighted different aspects of ECS therapy. ECS therapy may not be indicated for all patients as shown by a study that assessed whether ECS therapy initiated one year after the event of DVT would lower the incidence of PTS in patients without complaints but with reflux on duplex testing. No significant benefit of ECS therapy at this late time of onset was found. The incidence of PTS was low in both groups.¹⁰ One study so far assessed whether prolonged duration of ECS therapy was superior to 6 months of ECS therapy following an event of proximal DVT. In this study no significant difference in the incidence of PTS according to the CEAP classification was observed between the two treatment groups.¹¹

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3 The proposed IDEAL (individually tailored elastic compression against (=versus) longterm therapy)
4 DVT study is a non-inferiority trial and aims to demonstrate that the assessed alternative therapy
5 based on ECS for 6 months followed by individually prolonged ECS therapy based on Villalta scores is
6 non-inferior to the comparator ECS therapy for a standard duration of 24 months. In addition we are
7 interested to study the cost-effectiveness of individual tailoring of the duration of ECS therapy via a
8 cost-utility analysis (CUA) and we want to retrieve information on the patient's motivations for
9 compliance or non-compliance to therapy. Because compliance to therapy is one of the most
10 important prerequisites for successful ECS therapy, a discrete choice experiment (DCE) will be
11 performed in which patient preferences towards ECS therapy will be assessed, in order to reveal the
12 main obstacles for compliance to therapy. For this purpose, a DCE questionnaire will be send to a
13 subset of the population (300 patients) at approximately 3 months after DVT.

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23 The results of a recently published placebo controlled trial performed by Kahn et al. refuted the routine
24 wearing of ECS after DVT altogether.¹² This study showed no treatment effect at all from ECS therapy
25 in contrast to the large treatment effects found in previous non-placebo controlled trials.^{7 8} The
26 unexpected lack of effectiveness cannot be dismissed solely as a placebo effect. The compliance to
27 ECS therapy, a major determinant of effectiveness, was 55.6% after 24 months. This was less in
28 comparison to the previous trials by Brandjes and Prandoni, where compliance was up to 90%.^{7 8 12}
29 Although a per protocol analysis of the patients reporting regular stocking use yielded the same
30 outcome, this sub analysis may not be adequately powered to dismiss lack of compliance as an
31 important determinant of non-effectiveness.

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Based on current knowledge it is therefore understood that the standard application of ECS therapy is
questioned. Especially the benefit to individual patients and the optimal duration of ECS therapy were
never studied properly and as a result it is unclear which individual patients require therapy and for
how long.

The IDEAL DVT study aims to address these topics. In addition quality of life, patient preference
towards ECS therapy, compliance to therapy, as well as cost-effectiveness of ECS therapy will be
assessed.

The primary outcome of the IDEAL DVT study will be PTS at 24 months after the event. The
secondary outcomes will be: 1. Health Related Quality Of Life, measured by questionnaires (SF-36¹³,
EuroQOL-5D¹⁴, Dutch translated Veines-Qol¹⁵, 2. Costs¹⁶), 3. Recurrent thrombosis, according to

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3 criteria as published¹⁷ and assessed by objective tests, 4. VTE related death during follow-up,
4 assessed by an independent and blinded adjudication committee, 5. Patient preferences, assessed
5 with a Discrete Choice Experiment (DCE)¹⁸.
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10 The scope of the problem in the Netherlands

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12 In the Netherlands, each year around 25.000 patients experience a new event of DVT. In order to
13 prevent PTS, common practice is to prescribe custom fitted ECS therapy for 2 years for all patients.¹⁹

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15 ²⁰ ECS therapy is costly, demanding and sometimes even debilitating. Elderly patients can often not
16 apply the ECS by themselves but need help from family or they even need home care visits (7.5%).²¹⁻
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19 ²³ Total annual costs of ECS therapy roughly amounts to 2.5 million euro for stockings (25.000
20 patients*100 euro) and 21 million euro for home care (7.5%*25.000 patients*500 visits*20 euro).²¹⁻²³
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23 Moreover, the majority of patients do not experience any post thrombotic complaints.¹⁰ In the
24 Netherlands, over 10 million euro each year could be saved if ECS treatment would be individualized.
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28 Methods/Design

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30 A multicentre, single-blinded, allocation concealed, randomized, non-inferiority trial comparing
31 individually tailored duration of ECS therapy (intervention) with standard duration of 24 months ECS
32 therapy (control), for the prevention of PTS. Randomization will guarantee a balanced distribution of
33 patients within each patient group. Stratification will be performed on centre and potentially
34 confounding effects such as age, sex and body mass index. The study will be a multicenter study in
35 order to get a good representation of patients and to achieve sufficient patient numbers. The primary
36 outcome will be PTS at 24 months after the event; the observers will be blinded to the allocated
37 treatment arm. The allocation will be concealed from study personnel involved in assessing the leg
38 symptoms and rating the PTS scores. Both randomization and allocation concealment are used as
39 strategies against bias. The study is not double blinded; no inactive stockings will be used in the
40 comparator group. The use of sham stockings will very likely interfere with the quality of life and will
41 complicate the assessment of perceived differences between groups. Patients will be followed for the
42 entire study duration; incidence of recurrent DVT and VTE related death during the follow-up period
43 will be documented.
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Patients and treatment

Consecutive, consenting adults with an acute objectively documented proximal DVT of the leg, adequately treated with anticoagulant treatment and initial compression therapy according to a prespecified protocol are included in the study. Patients are included and randomized in the IDEAL DVT study within 2-6 weeks after DVT.

Exclusion criteria are:

- Previous DVT in the affected leg. Patients with a previous ipsilateral DVT might already have developed PTS after the first DVT.
- Recurrent DVT in the 6 months following inclusion, as it cannot be justified to advise these patients to discontinue ECS therapy 6 months after DVT.
- Pre-existent venous insufficiency (skin signs C3-C6 on CEAP score or requiring ECS therapy). Pre-existent venous insufficiency increases the risk of developing PTS and the majority of patients with venous insufficiency already chronically wear elastic compression stockings. In addition venous insufficiency is closely related to PTS and is therefore difficult to differentiate from PTS.
- Contraindication for ECS therapy such as intermittent claudication or clinical signs of leg ischemia or asymptomatic arterial insufficiency (a pulse deficit or bruit at sites of narrowing at physical examination).
- Active thrombolysis, as thrombolysis reduces the risk of PTS.
- Limited life expectancy (< 6 months), as the follow-up period is 2 years.

Patients are recruited from 12 hospitals in the Netherlands and 2 hospitals in Italy.

There is a prespecified protocol for the management of DVT in all participating centres.

In the initial acute phase after DVT, until the acute oedema has disappeared, one of three strategies will be applied. The leg is either bandaged with short stretch bandages to a compression of 30-40 mmHg, worn day and night and redressed twice per week; or a bandage stocking with 35mmHg compression is prescribed (Mediven Struva 35[®], Medi, Breda, the Netherlands), worn day and night; or no initial compression therapy is applied, according to the prespecified strategy of the hospital protocol. After the initial phase, a custom fitted, flat knitted, knee length graduated elastic compression stocking class III (ankle pressure 40 mmHg) is prescribed for all patients. The same brand and type (Mediven 550) of compression stocking is prescribed to all patients in all participating centres.

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3 Compression therapy with the elastic compression stocking is started immediately after the initial
4 phase, so there is no period without compression in between, with exception of the patients who do
5 not receive compression in the initial phase. Patients receive two new stockings every year. Patients
6 are advised to wear the stockings during the daytime.
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10 11 12 Procedures

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14 After obtaining written informed consent, randomization is performed centrally at the coordinating
15 study centre, the Maastricht University Medical centre. Patients are included and randomized within 2-
16 6 weeks after diagnosis of DVT. Patients are randomized to one of the two treatment arms. (Figure 1)
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18 A web-based randomisation program (TENALEA (Trans European Network for Clinical Trials
19 Services)) is used that executes blocked randomisation with stratification on centre-level and on
20 possible confounding patient characteristics such as age, sex, and Body Mass Index (<26 kg/m² - ≥26
21 kg/m²). Permuted blocks of randomly varying size are used to maintain balance of numbers in each
22 treatment group and to ensure allocation concealment.
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29 Information on allocation is only accessible to the study personnel at the coordinating study centre in
30 Maastricht, and patients will receive information about their allocation via the coordinating study
31 centre. The allocation will be concealed from study personnel involved in assessing the leg symptoms
32 and rating the PTS scores. Patients are not blinded by the use of sham stockings, because they may
33 influence quality of life, complicating the assessment of perceived differences between groups.
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35 Patients are asked not to reveal their treatment allocation to their own physician, and not to wear the
36 elastic compression stocking at the day of their outpatient clinic visits.
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44 All patients are advised to wear the elastic compression stocking during the first 6 months after DVT.
45 In the control group, all patients are instructed to wear the elastic compression stocking daily for a total
46 duration of 2 years. In the Intervention group, duration of ECS therapy is individually tailored based on
47 Villalta scores.²⁴ After the first 6 months therefore, there are three scenarios:
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- 51 (1) The Villalta score at both the 3 and 6-month follow-up visit is ≤ 4. Then the patient is advised
52 to discontinue ECS therapy.
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- 54 (2) The Villalta score at the 3-month follow-up visit is ≥ 5 the Villalta score at the 6 month follow-
55 up visit is ≤ 4. The patient is advised to continue the ECS therapy for another 6 months. If the
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3 Villalta score at the 12 month follow-up visit is ≤ 4 , the patient is allowed to discontinue the
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5 ECS therapy,

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7 (3) The Villalta score is ≥ 5 at both the 3 and 6 months follow-up visit. The patient is advised to
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9 continue the ECS therapy for a total duration of 24 months. (Figure 2)

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12 Using this algorithm the duration of ECS therapy is individually tailored in each patient. The decision
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14 on the duration of ECS therapy in patients in the intervention group is made centrally at the
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16 coordinating study centre, as only there the information on treatment allocation is available. The
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18 patient is informed about the decisions on the (dis) continuation of the ECS therapy by the
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20 coordinating centre.

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22 **When a patient develops symptoms and signs of PTS after discontinuation of ECS therapy, a**
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24 **predefined protocol is followed. If necessary, ECS treatment will be reinstated.**

25 26 27 Follow-up

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29 All patients are followed for 24 months after DVT. During these 24 months they visit the outpatient
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31 clinic 4 times: at 3, 6, 12, and 24 months after the DVT. At each follow-up visit the signs of PTS will be
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33 recorded and scored, by the study nurse or the treating physician, using the objective part of the
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35 Villalta clinical scale for PTS.²⁴ In case of intermittent leg complaints or signs or symptoms suspect of
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37 recurrent VTE, patients are instructed to visit their treating physician. Study documentation will be
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39 filled out and adverse events will be recorded. The CCMO (central committee human related research)
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41 will be notified in case of serious adverse events or death.

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43 The patient is asked to fill out 5 questionnaires: at baseline, and 3, 6, 12 and 24 months later. All
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45 questionnaires will be offered as a web based application, each patient will have a unique personal
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47 entry code. For patients who are not able or willing to use the electronic questionnaires, a paper
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49 version will be available. The first questionnaire is filled out shortly after inclusion (4-6 weeks after
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51 DVT) and the subsequent questionnaires are filled out the day before each follow-up visit. All
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53 questionnaires contain the subjective part of the Villalta clinical scale for PTS²⁴, questions on ECS
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55 compliance, a cost questionnaire¹⁶, and three health related quality of life (HRQOL) questionnaires:
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57 the Dutch translated Veines-Qol¹⁵, the SF-36¹³, and the EuroQOL-5D¹⁴. In a subset of the study
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59 population patient preferences regarding elastic compression therapy will be analysed, by conducting
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3 a discrete choice experiment (DCE). For this purpose, a DCE questionnaire will be send to a subset of
4 the population at approximately 3 months after DVT.
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7 Compliance to ECS therapy is monitored in two ways. Each questionnaire contains a question on
8 compliance to the advised version of ECS therapy. Because compliance and adherence to therapy is
9 of crucial importance the number of contact moments for the assessment of compliance with ECS
10 therapy will be increased by adding telephone contacts to the regular clinical visits. Study-supporting
11 staff will make computer-assisted random telephone calls during the entire follow-up period to both the
12 patients in the group with the 2-year ECS intervention and to patients in the group with individualized
13 ECS therapy. The telephone calls will be made randomly to create a surprise effect (patients are off
14 guard) and to allow for a distribution of contacts over the entire study period. Per patient 3 extra
15 contact moments will be created. A standard questionnaire will be used to assess compliance and to
16 address reasons for non-compliance. Crossover to another therapy arm will be discussed and
17 discouraged.
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29 Outcomes

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31 The primary outcome is the proportion of patients with PTS at the end of follow-up, 24 months after
32 DVT. PTS is defined as a Villalta score of ≥ 5 at two consecutive visits that are at least three months
33 apart. **The time point of the second Villalta score of ≥ 5 will be considered the time point of PTS**
34 **diagnosis.** Although the consensus is to diagnose PTS at the 6-month visit or later based on one
35 single Villalta score ≥ 5 ²⁵, we modelled this study after the preceding management study in which two
36 consecutive Villalta scores ≥ 5 were needed for the diagnosis PTS. We observed that a proportion of
37 patients (about 12%) had fluctuating Villalta scores beyond 6 months after the acute event of DVT.⁹
38 Assigning the diagnosis based on one single score ≥ 5 would therefore lead to misclassification and
39 overestimation of the PTS incidence. The Villalta scores at 6 months will be available; therefore also
40 the proportion of patients with PTS according to the consensus scoring method will be presented.
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51 Secondary outcomes include:

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53 1. HRQOL, measured by questionnaires (SF-36¹³, EuroQOL-5D¹⁴, Dutch translated Veines-Qol¹⁵), 2.
54 Costs¹⁶, 3. Recurrent thrombosis, according to criteria as published¹⁷ and assessed by objective
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3 tests, 4. VTE related death during follow-up, assessed by an independent and blinded adjudication
4 committee, 5. Patient preferences, assessed with a Discrete Choice Experiment (DCE)¹⁸.

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8 Since both effects on costs and generic health-related quality of life are to be expected, the method of
9 economic evaluation is a cost-utility analysis (CUA). The analysis will be from a societal perspective.
10 The primary effect parameter is generic health-related quality of life, measured in quality adjusted life
11 years (QALYs). We will perform two analyses: a trial based CUA with a time horizon of two years
12 (identical to the duration of follow up in the clinical study), and a model-based CUA with a lifelong time
13 horizon. For the latter, we will follow the guidelines of good modelling.²⁶ We will be able to adapt a
14 Markov model for diagnostic strategies in DVT, which was developed by our group earlier.²⁷ Costs in
15 the economic analyses include direct health care costs (medical costs for prevention, diagnostics,
16 therapy, rehabilitation and care), direct non-health care costs (travel costs) and indirect costs
17 (productivity loss). Utilities will be calculated from the responses on the EQ-5D and SF36 classification
18 systems using the available multi-attribute utility functions.^{28 29} Incremental cost-utility ratios will be
19 calculated, and non-parametric bootstrap analyses will be used to quantify the uncertainty surrounding
20 the cost-utility ratio of the trial-based analysis. Sensitivity analyses and subgroup analyses will be
21 performed, to assess the impact of variation in parameters and heterogeneity of the patient population.
22 ECS therapy has several disadvantages for the patients (stockings are uncomfortable, ugly, and
23 difficult to put on and off), while duration and effectiveness are uncertain. A DCE will be conducted to
24 assess the patient preferences regarding ECS therapy, providing insight in the trade-offs patients
25 make between characteristics of the therapy when deciding to wear the stocking or not. Duration of
26 ECS therapy is one of the characteristics. Data will be analysed using multinomial logit models and
27 mixed logit models.(Nlogit, Econometric Software)

28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 Sample size calculation

48 The proposed study is a non-inferiority trial and aims to demonstrate that the assessed alternative
49 therapy based on ECS for 6 months followed by individually prolonged ECS therapy based on Villalta
50 scores is not worse than the comparator ECS therapy for a standard duration of 24 months, by more
51 than the prespecified amount of 7.5% (the non-inferiority margin). The published incidence of PTS
52 following two years of ECS lies between 20 and 30%. (Prandoni 24.5% (95% CI 15.6- 33.4), Brandjes
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3 20% (95% CI 12.4-29.2)^{7 8} As it is statistically impossible to demonstrate equivalence (prove the H0 of
4 no difference), Blackwelder proposed a one sided significance test to reject the null hypothesis by a
5 clinically acceptable amount.³⁰ If we allow a difference of 7.5% in the outcome PTS between the group
6 with ECS for 2 years and the group with the alternative therapy, 70% of the effect will be preserved.
7
8 This proportion of loss in efficacy is customarily accepted in controlled randomized clinical trials. At a
9
10 one sided significance level of 0.05 and a power of 80%, with a ratio of 1, a total of 847 patients is
11
12 needed to provide sufficient patients for an adequately powered trial.^{30 31} Loss to follow-up of patients
13
14 is expected to be less than 2% since the intervention does not have an invasive nature. Therefore, a
15
16 total of 864 patients are needed (432 patients per treatment arm).
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20 21 Statistical analysis

22 Descriptive statistics of the total population and of the two treatment groups separately will be
23
24 computed to provide baseline characteristics of the patients in both treatment arms.
25

26 For the primary outcome PTS, univariate analysis of all proportions will be performed with logistic
27
28 regression (chi-squared) analysis. Kaplan-Meier method will be used to calculate the cumulative
29
30 incidences of PTS, adjusted for centre, to compare incidence rates between the two treatment arms.
31
32 Patients who die or are lost to follow-up will be censored at their last visit. ANOVA will be applied to
33
34 assess changes over time, **by comparing** different outcome measures **at the different time points of**
35
36 **follow-up.**

37 Hazard ratio's and 95% confidence intervals for both treatment arms will be calculated using Cox
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39 regression models. Hazard ratio's will be **stratified for centre** and adjusted for age, sex, **BMI**, clinical
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41 presentation of DVT, and extent of the index deep vein thrombosis.
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45 Interim analysis (safety)

46 A prespecified safety analysis will be performed when 50% of the subjects have completed the 2-year
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48 follow-up. The analysis will be performed by the coordinating centre, and supervised by the principal
49
50 investigators. The safety analysis will be performed to assess significant enhanced risk of PTS or
51
52 excess morbidity/mortality in the intervention arm of the study population. Fisher's exact test will be
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54 performed to compare incidence of PTS at a significance level of 0.05 (two sided). The study can
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56 be stopped in case of significant excess morbidity/mortality in the alternative treatment arm.
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5 Ethical considerations

6 The medical ethical committees of all participating hospitals in the Netherlands and Italy approved this
7 study. All patients are extensively informed about the study, and written informed consent is obtained
8 from all participating patients.
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11 12 13 **Discussion**

14 Based on current knowledge the standard application of ECS therapy after DVT is questioned. The
15 definitive answer on the usefulness of ECS therapy for the prevention of PTS is not yet provided.
16 Therefore the need for the IDEAL DVT study remains unchanged. The benefit to individual patients
17 and the optimal duration of ECS therapy were never studied properly and as a result it is unclear
18 which individual patients require therapy and for how long. The IDEAL DVT study will address the
19 central questions that remain unanswered: What individual patients do benefit from ECS therapy and
20 what is the optimal individual treatment duration? The study that we plan to perform is not only
21 innovative; for the first time individual tailoring of duration of ECS therapy will be investigated, but also
22 it will provide unique additional knowledge on the safety, effectiveness and cost- effectiveness of this
23 approach. The IDEAL DVT study started including patients March 2011 and is currently on-going.
24 Recruitment is expected to be terminated within 1 year. As the follow-up is 2 years, the results are
25 expected within 3 years.
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Trial status

The IDEAL DVT study is currently in progress. Patient recruitment started March 15th 2011 and is still on-going.

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We especially acknowledge the participating investigators.

Competing interests

The authors declare that they have no competing interests.

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Contributions

AtC wrote the protocol and designed the study, the other authors MJ (cost-effectiveness research), MP (study design/statistics) and HtC (study design) contributed. AB is a PhD student and coordinator of the trial.

Ethics approval

Maastricht University Medical Centre.

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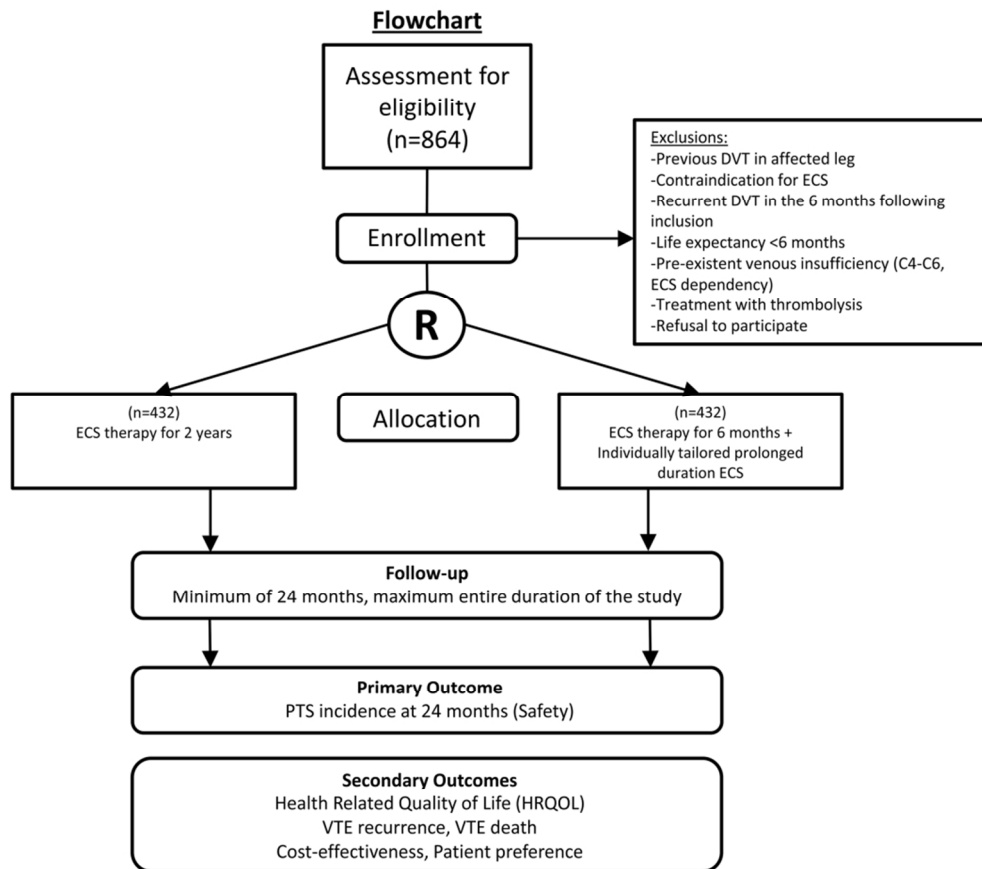


Figure 1. Study flow diagram
90x79mm (300 x 300 DPI)

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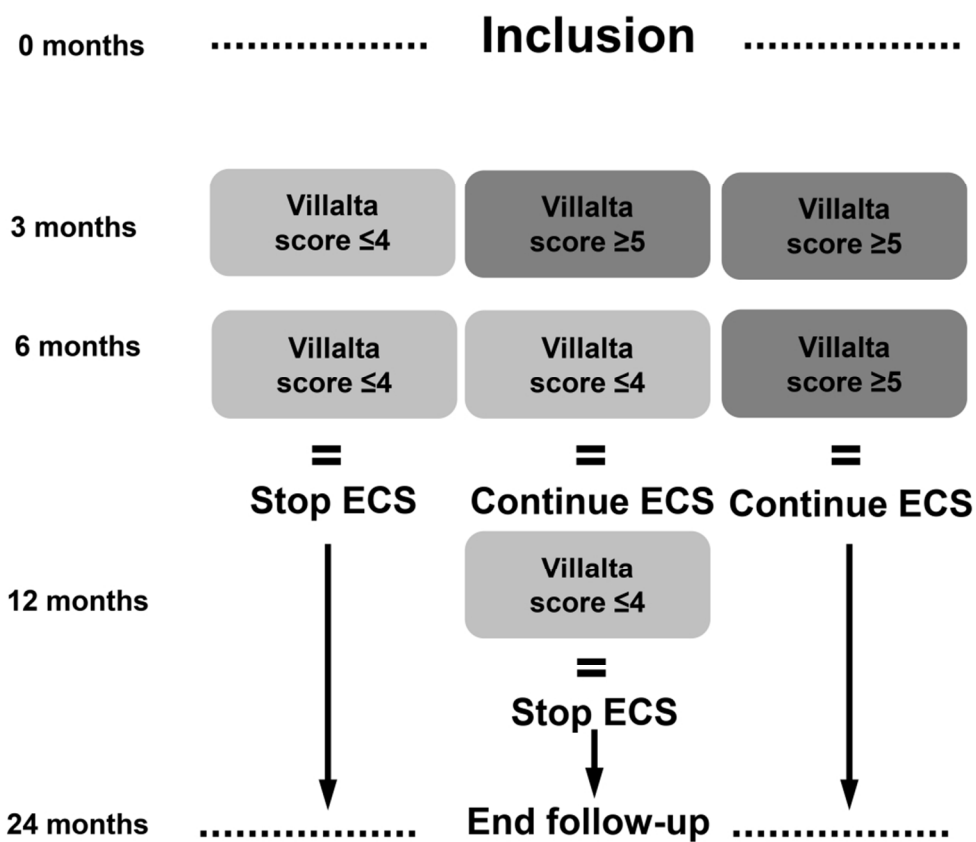


Figure 2. Algorithm individually tailored ECS therapy
90x77mm (300 x 300 DPI)

BMJ Open

The IDEAL DVT study, individualized duration elastic compression therapy against long-term duration of therapy for the prevention of post thrombotic syndrome, a randomized controlled trial

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Haematology (incl blood transfusion), Health economics
Keywords:	Post thrombotic syndrome, Deep vein thrombosis, Elastic compression stocking therapy, Protocol, RCT

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Manuscripts

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3 Study Protocol

4 The IDEAL DVT study, individualized duration elastic compression therapy against long-term duration
5 of therapy for the prevention of post thrombotic syndrome, a randomized controlled trial
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49 Key words: Post thrombotic syndrome, deep vein thrombosis, elastic compression stocking therapy,
50 protocol, RCT
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53 Word count: 3345
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Abstract**Introduction:**

Post thrombotic syndrome (PTS) is a serious complication of deep vein thrombosis (DVT) of the leg that affects 20-50% of patients. Once a patient experiences PTS there is no treatment that effectively reduces the debilitating complaints. Two randomized controlled trials showed that elastic compression stocking (ECS) therapy after DVT for 24 months can reduce the incidence of PTS by 50%. However, it is unclear whether all patients benefit to the same extent from ECS therapy or what the optimal duration of therapy for individual patients should be. ECS therapy is costly, inconvenient, demanding and sometimes even debilitating. Tailoring therapy to individual needs could save substantial costs. The objective of the IDEAL DVT study therefore is to evaluate whether tailoring the duration of ECS therapy on signs and symptoms of the individual patient is a safe and effective method to prevent PTS, compared to standard ECS therapy.

Methods and analysis:

A multicentre, single-blinded, allocation concealed, randomized, non-inferiority trial. A total of 864 consecutive patients with acute objectively documented proximal DVT of the leg are randomized to either standard duration of 24 months or tailored duration of ECS therapy following an initial therapeutic period of 6 months. Signs and symptoms of PTS are recorded at regular clinic visits. Furthermore, quality of life, costs, patient preferences and compliance are measured. The primary outcome is the proportion of patients with PTS at 24 months.

Ethics and dissemination:

Based on current knowledge the standard application of ECS therapy is questioned. The IDEAL DVT study will address the central questions that remain unanswered: What individual patients do benefit from ECS therapy and what is the optimal individual treatment duration? Primary ethics approval was received from the Maastricht University Medical Centre.

Results of the study will be disseminated via peer-reviewed publications and presentations at scientific conferences.

Trial Registration number:

NCT01429714 and NTR 2597

Background

After deep vein thrombosis (DVT) 20-50% of patients develop post thrombotic syndrome (PTS). PTS is a chronic condition, characterized by leg complaints such as pain; heaviness; cramps; aching; tingling; and leg signs due to venous insufficiency, evolving in severe cases to venous ulceration of the leg that was affected by the DVT.¹⁻⁵ PTS is a serious affliction, with substantial impact on quality of life and costs.^{2,6} Because an effective therapy is lacking, prevention of PTS is of major importance. Up till now, elastic compression stocking (ECS) therapy after DVT has been the mainstay of PTS prevention. The evidence sustaining the value of ECS therapy following acute DVT is derived from 2 randomized clinical trials, which showed that incidences of PTS were reduced by approximately 50%, with application of ECS therapy for 24 months.^{7,8} However, based on these trials it is still undecided whether all patients benefit to the same extent from ECS therapy or what the optimal duration of ECS therapy for individual patients should be. We have previously assessed the safety of shortened duration of ECS therapy based on individual patient clinical scores in a management study of 125 patients, and we have shown that tailoring the duration of ECS therapy based on the signs and symptoms of the individual patient after an initial treatment period of 6 months, is a safe strategy to prevent PTS. We found that 50% of our patients did not need ECS therapy for as long as 2 years, while the overall incidence of PTS was 21.1% (95% CI 13.5- 28.7).⁹ This incidence is comparable to published incidences after 24 months ECS therapy.^{7,8} While this was a prospective management cohort study with an open character and therefore prone to bias, the results of this study need to be confirmed by an adequately powered randomized controlled trial.

There have been other studies that highlighted different aspects of ECS therapy. ECS therapy may not be indicated for all patients as shown by a study that assessed whether ECS therapy initiated one year after the event of DVT would lower the incidence of PTS in patients without complaints but with reflux on duplex testing. No significant benefit of ECS therapy at this late time of onset was found. The incidence of PTS was low in both groups.¹⁰ One study so far assessed whether prolonged duration of ECS therapy was superior to 6 months of ECS therapy following an event of proximal DVT. In this study no significant difference in the incidence of PTS according to the CEAP classification was observed between the two treatment groups.¹¹

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3 The proposed IDEAL (individually tailored elastic compression against (=versus) longterm therapy)
4 DVT study is a non-inferiority trial and aims to demonstrate that the assessed alternative therapy
5 based on ECS for 6 months followed by individually prolonged ECS therapy based on Villalta scores is
6 non-inferior to the comparator ECS therapy for a standard duration of 24 months. In addition we are
7 interested to study the cost-effectiveness of individual tailoring of the duration of ECS therapy via a
8 cost-utility analysis (CUA) and we want to retrieve information on the patient's motivations for
9 compliance or non-compliance to therapy. Because compliance to therapy is one of the most
10 important prerequisites for successful ECS therapy, a discrete choice experiment (DCE) will be
11 performed in which patient preferences towards ECS therapy will be assessed, in order to reveal the
12 main obstacles for compliance to therapy. For this purpose, a DCE questionnaire will be send to a
13 subset of the population (300 patients) at approximately 3 months after DVT.

14
15 The results of a recently published placebo controlled trial performed by Kahn et al. refuted the routine
16 wearing of ECS after DVT altogether.¹² This study showed no treatment effect at all from ECS therapy
17 in contrast to the large treatment effects found in previous non-placebo controlled trials.^{7 8} The
18 unexpected lack of effectiveness cannot be dismissed solely as a placebo effect. The compliance to
19 ECS therapy, a major determinant of effectiveness, was 55.6% after 24 months. This was less in
20 comparison to the previous trials by Brandjes and Prandoni, where compliance was up to 90%.^{7 8 12}
21 Although a per protocol analysis of the patients reporting regular stocking use yielded the same
22 outcome, this sub analysis may not be adequately powered to dismiss lack of compliance as an
23 important determinant of non-effectiveness.

24
25 Based on current knowledge it is therefore understood that the standard application of ECS therapy is
26 questioned. Especially the benefit to individual patients and the optimal duration of ECS therapy were
27 never studied properly and as a result it is unclear which individual patients require therapy and for
28 how long.

29
30 The IDEAL DVT study aims to address these topics. In addition quality of life, patient preference
31 towards ECS therapy, compliance to therapy, as well as cost-effectiveness of ECS therapy will be
32 assessed.

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34 The primary outcome of the IDEAL DVT study will be PTS at 24 months after the event. The
35 secondary outcomes will be: 1. Health Related Quality Of Life, measured by questionnaires (SF-36¹³,
36 EuroQOL-5D¹⁴, Dutch translated Veines-Qol¹⁵, 2. Costs¹⁶), 3. Recurrent thrombosis, according to
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3 criteria as published¹⁷ and assessed by objective tests, 4. VTE related death during follow-up,
4 assessed by an independent and blinded adjudication committee, 5. Patient preferences, assessed
5 with a Discrete Choice Experiment (DCE)¹⁸.
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10 The scope of the problem in the Netherlands

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12 In the Netherlands, each year around 25.000 patients experience a new event of DVT. In order to
13 prevent PTS, common practice is to prescribe custom fitted ECS therapy for 2 years for all patients.¹⁹

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15 ²⁰ ECS therapy is costly, demanding and sometimes even debilitating. Elderly patients can often not
16 apply the ECS by themselves but need help from family or they even need home care visits (7.5%).²¹⁻
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19 ²³ Total annual costs of ECS therapy roughly amounts to 2.5 million euro for stockings (25.000
20 patients*100 euro) and 21 million euro for home care (7.5%*25.000 patients*500 visits*20 euro).²¹⁻²³
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23 Moreover, the majority of patients do not experience any post thrombotic complaints.¹⁰ In the
24 Netherlands, over 10 million euro each year could be saved if ECS treatment would be individualized.
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28 **Methods/Design**

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30 A multicentre, single-blinded, allocation concealed, randomized, non-inferiority trial comparing
31 individually tailored duration of ECS therapy (intervention) with standard duration of 24 months ECS
32 therapy (control), for the prevention of PTS. Randomization will guarantee a balanced distribution of
33 patients within each patient group. Stratification will be performed on centre and potentially
34 confounding effects such as age, sex and body mass index. The study will be a multicenter study in
35 order to get a good representation of patients and to achieve sufficient patient numbers. The primary
36 outcome will be PTS at 24 months after the event; the observers will be blinded to the allocated
37 treatment arm. The allocation will be concealed from study personnel involved in assessing the leg
38 symptoms and rating the PTS scores. Both randomization and allocation concealment are used as
39 strategies against bias. The study is not double blinded; no inactive stockings will be used in the
40 comparator group. The use of sham stockings will very likely interfere with the quality of life and will
41 complicate the assessment of perceived differences between groups. Patients will be followed for the
42 entire study duration; incidence of recurrent DVT and VTE related death during the follow-up period
43 will be documented.
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Patients and treatment

Consecutive, consenting adults with an acute objectively documented proximal DVT of the leg, adequately treated with anticoagulant treatment and initial compression therapy according to a prespecified protocol are included in the study. Patients are included and randomized in the IDEAL DVT study within 2-6 weeks after DVT.

Exclusion criteria are:

- Previous DVT in the affected leg. Patients with a previous ipsilateral DVT might already have developed PTS after the first DVT.
- Recurrent DVT in the 6 months following inclusion, as it cannot be justified to advise these patients to discontinue ECS therapy 6 months after DVT.
- Pre-existent venous insufficiency (skin signs C3-C6 on CEAP score or requiring ECS therapy). Pre-existent venous insufficiency increases the risk of developing PTS and the majority of patients with venous insufficiency already chronically wear elastic compression stockings. In addition venous insufficiency is closely related to PTS and is therefore difficult to differentiate from PTS.
- Contraindication for ECS therapy such as intermittent claudication or clinical signs of leg ischemia or asymptomatic arterial insufficiency (a pulse deficit or bruit at sites of narrowing at physical examination).
- Active thrombolysis, as thrombolysis reduces the risk of PTS.
- Limited life expectancy (< 6 months), as the follow-up period is 2 years.

Patients are recruited from 12 hospitals in the Netherlands and 2 hospitals in Italy.

There is a prespecified protocol for the management of DVT in all participating centres.

In the initial acute phase after DVT, until the acute oedema has disappeared, one of three strategies will be applied. The leg is either bandaged with short stretch bandages to a compression of 30-40 mmHg, worn day and night and redressed twice per week; or a bandage stocking with 35mmHg compression is prescribed (Mediven Struva 35[®], Medi, Breda, the Netherlands), worn day and night; or no initial compression therapy is applied, according to the prespecified strategy of the hospital protocol. After the initial phase, a custom fitted, flat knitted, knee length graduated elastic compression stocking class III (ankle pressure 40 mmHg) is prescribed for all patients. The same brand and type (Mediven 550) of compression stocking is prescribed to all patients in all participating centres.

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3 Compression therapy with the elastic compression stocking is started immediately after the initial
4 phase, so there is no period without compression in between, with exception of the patients who do
5 not receive compression in the initial phase. Patients receive two new stockings every year. Patients
6 are advised to wear the stockings during the daytime.
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10 11 12 Procedures

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14 After obtaining written informed consent, randomization is performed centrally at the coordinating
15 study centre, the Maastricht University Medical centre. Patients are included and randomized within 2-
16 6 weeks after diagnosis of DVT. Patients are randomized to one of the two treatment arms. (Figure 1)
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18 A web-based randomisation program (TENALEA (Trans European Network for Clinical Trials
19 Services)) is used that executes blocked randomisation with stratification on centre-level and on
20 possible confounding patient characteristics such as age, sex, and Body Mass Index ($<26 \text{ kg/m}^2$ - ≥ 26
21 kg/m^2). Permuted blocks of randomly varying size are used to maintain balance of numbers in each
22 treatment group and to ensure allocation concealment.
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29 Information on allocation is only accessible to the study personnel at the coordinating study centre in
30 Maastricht, and patients will receive information about their allocation via the coordinating study
31 centre. The allocation will be concealed from study personnel involved in assessing the leg symptoms
32 and rating the PTS scores. Patients are not blinded by the use of sham stockings, because they may
33 influence quality of life, complicating the assessment of perceived differences between groups.
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35 Patients are asked not to reveal their treatment allocation to their own physician, and not to wear the
36 elastic compression stocking at the day of their outpatient clinic visits.
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44 All patients are advised to wear the elastic compression stocking during the first 6 months after DVT.
45 In the control group, all patients are instructed to wear the elastic compression stocking daily for a total
46 duration of 2 years. In the Intervention group, duration of ECS therapy is individually tailored based on
47 Villalta scores.²⁴ After the first 6 months therefore, there are three scenarios:
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- 51 (1) The Villalta score at both the 3 and 6-month follow-up visit is ≤ 4 . Then the patient is advised
52 to discontinue ECS therapy.
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- 54 (2) The Villalta score at the 3-month follow-up visit is ≥ 5 the Villalta score at the 6 month follow-
55 up visit is ≤ 4 . The patient is advised to continue the ECS therapy for another 6 months. If the
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3 Villalta score at the 12 month follow-up visit is ≤ 4 , the patient is allowed to discontinue the
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5 ECS therapy,

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7 (3) The Villalta score is ≥ 5 at both the 3 and 6 months follow-up visit. The patient is advised to
8
9 continue the ECS therapy for a total duration of 24 months. (Figure 2)

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12 Using this algorithm the duration of ECS therapy is individually tailored in each patient. The decision
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14 on the duration of ECS therapy in patients in the intervention group is made centrally at the
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16 coordinating study centre, as only there the information on treatment allocation is available. The
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18 patient is informed about the decisions on the (dis) continuation of the ECS therapy by the
19
20 coordinating centre.

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22 When a patient develops symptoms and signs of PTS after discontinuation of ECS therapy, a
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24 predefined protocol is followed. If necessary, ECS treatment will be reinstated.

25 26 27 Follow-up

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29 All patients are followed for 24 months after DVT. During these 24 months they visit the outpatient
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31 clinic 4 times: at 3, 6, 12, and 24 months after the DVT. At each follow-up visit the signs of PTS will be
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33 recorded and scored, by the study nurse or the treating physician, using the objective part of the
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35 Villalta clinical scale for PTS.²⁴ In case of intermittent leg complaints or signs or symptoms suspect of
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37 recurrent VTE, patients are instructed to visit their treating physician. Study documentation will be
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39 filled out and adverse events will be recorded. The CCMO (central committee human related research)
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41 will be notified in case of serious adverse events or death.

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43 The patient is asked to fill out 5 questionnaires: at baseline, and 3, 6, 12 and 24 months later. All
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45 questionnaires will be offered as a web based application, each patient will have a unique personal
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47 entry code. For patients who are not able or willing to use the electronic questionnaires, a paper
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49 version will be available. The first questionnaire is filled out shortly after inclusion (4-6 weeks after
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51 DVT) and the subsequent questionnaires are filled out the day before each follow-up visit. All
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53 questionnaires contain the subjective part of the Villalta clinical scale for PTS²⁴, questions on ECS
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55 compliance, a cost questionnaire¹⁶, and three health related quality of life (HRQOL) questionnaires:
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57 the Dutch translated Veines-Qol¹⁵, the SF-36¹³, and the EuroQOL-5D¹⁴. In a subset of the study
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59 population patient preferences regarding elastic compression therapy will be analysed, by conducting
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3 a discrete choice experiment (DCE). For this purpose, a DCE questionnaire will be send to a subset of
4 the population at approximately 3 months after DVT.
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7 Compliance to ECS therapy is monitored in two ways. Each questionnaire contains a question on
8 compliance to the advised version of ECS therapy. Because compliance and adherence to therapy is
9 of crucial importance the number of contact moments for the assessment of compliance with ECS
10 therapy will be increased by adding telephone contacts to the regular clinical visits. Study-supporting
11 staff will make computer-assisted random telephone calls during the entire follow-up period to both the
12 patients in the group with the 2-year ECS intervention and to patients in the group with individualized
13 ECS therapy. The telephone calls will be made randomly to create a surprise effect (patients are off
14 guard) and to allow for a distribution of contacts over the entire study period. Per patient 3 extra
15 contact moments will be created. A standard questionnaire will be used to assess compliance and to
16 address reasons for non-compliance. Crossover to another therapy arm will be discussed and
17 discouraged.
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29 Outcomes

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31 The primary outcome is the proportion of patients with PTS at the end of follow-up, 24 months after
32 DVT. PTS is defined as a Villalta score of ≥ 5 at two consecutive visits that are at least three months
33 apart. The time point of the second Villalta score of ≥ 5 will be considered the time point of PTS
34 diagnosis. Although the consensus is to diagnose PTS at the 6-month visit or later based on one
35 single Villalta score ≥ 5 ²⁵, we modelled this study after the preceding management study in which two
36 consecutive Villalta scores ≥ 5 were needed for the diagnosis PTS. We observed that a proportion of
37 patients (about 12%) had fluctuating Villalta scores beyond 6 months after the acute event of DVT.⁹
38 Assigning the diagnosis based on one single score ≥ 5 would therefore lead to misclassification and
39 overestimation of the PTS incidence. The Villalta scores at 6 months will be available; therefore also
40 the proportion of patients with PTS according to the consensus scoring method will be presented.
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51 Secondary outcomes include:

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53 1. HRQOL, measured by questionnaires (SF-36¹³, EuroQOL-5D¹⁴, Dutch translated Veines-Qol¹⁵), 2.
54 Costs¹⁶, 3. Recurrent thrombosis, according to criteria as published¹⁷ and assessed by objective
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3 tests, 4. VTE related death during follow-up, assessed by an independent and blinded adjudication
4 committee, 5. Patient preferences, assessed with a Discrete Choice Experiment (DCE)¹⁸.
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8 Since both effects on costs and generic health-related quality of life are to be expected, the method of
9 economic evaluation is a cost-utility analysis (CUA). The analysis will be from a societal perspective.
10 The primary effect parameter is generic health-related quality of life, measured in quality adjusted life
11 years (QALYs). We will perform two analyses: a trial based CUA with a time horizon of two years
12 (identical to the duration of follow up in the clinical study), and a model-based CUA with a lifelong time
13 horizon. For the latter, we will follow the guidelines of good modelling.²⁶ We will be able to adapt a
14 Markov model for diagnostic strategies in DVT, which was developed by our group earlier.²⁷ Costs in
15 the economic analyses include direct health care costs (medical costs for prevention, diagnostics,
16 therapy, rehabilitation and care), direct non-health care costs (travel costs) and indirect costs
17 (productivity loss). Utilities will be calculated from the responses on the EQ-5D and SF36 classification
18 systems using the available multi-attribute utility functions.^{28 29} Incremental cost-utility ratios will be
19 calculated, and non-parametric bootstrap analyses will be used to quantify the uncertainty surrounding
20 the cost-utility ratio of the trial-based analysis. Sensitivity analyses and subgroup analyses will be
21 performed, to assess the impact of variation in parameters and heterogeneity of the patient population.
22 ECS therapy has several disadvantages for the patients (stockings are uncomfortable, ugly, and
23 difficult to put on and off), while duration and effectiveness are uncertain. A DCE will be conducted to
24 assess the patient preferences regarding ECS therapy, providing insight in the trade-offs patients
25 make between characteristics of the therapy when deciding to wear the stocking or not. Duration of
26 ECS therapy is one of the characteristics. Data will be analysed using multinomial logit models and
27 mixed logit models. (Nlogit, Econometric Software)
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47 Sample size calculation

48 The proposed study is a non-inferiority trial and aims to demonstrate that the assessed alternative
49 therapy based on ECS for 6 months followed by individually prolonged ECS therapy based on Villalta
50 scores is not worse than the comparator ECS therapy for a standard duration of 24 months, by more
51 than the prespecified amount of 7.5% (the non-inferiority margin). The published incidence of PTS
52 following two years of ECS lies between 20 and 30%. (Prandoni 24.5% (95% CI 15.6- 33.4), Brandjes
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3 20% (95% CI 12.4-29.2)^{7 8} As it is statistically impossible to demonstrate equivalence (prove the H0 of
4 no difference), Blackwelder proposed a one sided significance test to reject the null hypothesis by a
5 clinically acceptable amount.³⁰ If we allow a difference of 7.5% in the outcome PTS between the group
6 with ECS for 2 years and the group with the alternative therapy, 70% of the effect will be preserved.
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8 This proportion of loss in efficacy is customarily accepted in controlled randomized clinical trials. At a
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10 one sided significance level of 0.05 and a power of 80%, with a ratio of 1, a total of 847 patients is
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12 needed to provide sufficient patients for an adequately powered trial.^{30 31} Loss to follow-up of patients
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14 is expected to be less than 2% since the intervention does not have an invasive nature. Therefore, a
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16 total of 864 patients are needed (432 patients per treatment arm).
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21 Statistical analysis

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23 Descriptive statistics of the total population and of the two treatment groups separately will be
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25 computed to provide baseline characteristics of the patients in both treatment arms.

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27 For the primary outcome PTS, univariate analysis of all proportions will be performed with logistic
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29 regression (chi-squared) analysis. Kaplan-Meier method will be used to calculate the cumulative
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31 incidences of PTS, adjusted for centre, to compare incidence rates between the two treatment arms.
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33 Patients who die or are lost to follow-up will be censored at their last visit. ANOVA will be applied to
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35 assess changes over time, by comparing different outcome measures at the different time points of
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37 follow-up.

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39 Hazard ratio's and 95% confidence intervals for both treatment arms will be calculated using Cox
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41 regression models. Hazard ratio's will be stratified for centre and adjusted for age, sex, BMI, clinical
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43 presentation of DVT, and extent of the index deep vein thrombosis.
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45 Interim analysis (safety)

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47 A prespecified safety analysis will be performed when 50% of the subjects have completed the 2-year
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49 follow-up. The analysis will be performed by the coordinating centre, and supervised by the principal
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51 investigators. The safety analysis will be performed to assess significant enhanced risk of PTS or
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53 excess morbidity/mortality in the intervention arm of the study population. Fisher's exact test will be
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55 performed to compare incidence of PTS at a significance level of 0.05 (two sided). The study can
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57 be stopped in case of significant excess morbidity/mortality in the alternative treatment arm.
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Ethical considerations

The medical ethical committees of all participating hospitals in the Netherlands and Italy approved this study. All patients are extensively informed about the study, and written informed consent is obtained from all participating patients.

The IDEAL DVT study started including patients at 11th of March 2011 and inclusion is currently ongoing. Recruitment is expected to be terminated in January 2015. As the follow-up is 2 years, the results are expected within 3 years, in January 2017.

Discussion

Based on current knowledge the standard application of ECS therapy after DVT is questioned. The definitive answer on the usefulness of ECS therapy for the prevention of PTS is not yet provided. Therefore the need for the IDEAL DVT study remains unchanged. The benefit to individual patients and the optimal duration of ECS therapy were never studied properly and as a result it is unclear which individual patients require therapy and for how long. The IDEAL DVT study will address the central questions that remain unanswered: What individual patients do benefit from ECS therapy and what is the optimal individual treatment duration? The study that we plan to perform is not only innovative; for the first time individual tailoring of duration of ECS therapy will be investigated, but also it will provide unique additional knowledge on the safety, effectiveness and cost-effectiveness of this approach.

Trial status

The IDEAL DVT study is currently in progress. Patient recruitment started March 15th 2011 and is still on-going.

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Competing interests

The authors declare that they have no competing interests.

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Contributions

AtC wrote the protocol and designed the study, the other authors MJ (cost-effectiveness research), MP (study design/statistics) and HtC (study design) contributed. AB is a PhD student and coordinator of the trial.

Ethics approval

Maastricht University Medical Centre.

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29
30 **FIGURE LEGENDS**

32 Figure 1. Study flow diagram

34 Figure 2. Algorithm individually tailored ECS therapy

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7 Study Protocol

8 The IDEAL DVT study, individualized duration elastic compression therapy against long-term duration
9 of therapy for the prevention of post thrombotic syndrome, a randomized controlled trial
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47 Key words: Post thrombotic syndrome, deep vein thrombosis, elastic compression stocking therapy,
48 protocol, RCT
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50 Word count: 3345
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Abstract**Introduction:**

Post thrombotic syndrome (PTS) is a serious complication of deep vein thrombosis (DVT) of the leg that affects 20-50% of patients. Once a patient experiences PTS there is no treatment that effectively reduces the debilitating complaints. Two randomized controlled trials showed that elastic compression stocking (ECS) therapy after DVT for 24 months can reduce the incidence of PTS by 50%. However, it is unclear whether all patients benefit to the same extent from ECS therapy or what the optimal duration of therapy for individual patients should be. ECS therapy is costly, inconvenient, demanding and sometimes even debilitating. Tailoring therapy to individual needs could save substantial costs. The objective of the IDEAL DVT study therefore is to evaluate whether tailoring the duration of ECS therapy on signs and symptoms of the individual patient is a safe and effective method to prevent PTS, compared to standard ECS therapy.

Methods and analysis:

A multicentre, single-blinded, allocation concealed, randomized, non-inferiority trial. A total of 864 consecutive patients with acute objectively documented proximal DVT of the leg are randomized to either standard duration of 24 months or tailored duration of ECS therapy following an initial therapeutic period of 6 months. Signs and symptoms of PTS are recorded at regular clinic visits. Furthermore, quality of life, costs, patient preferences and compliance are measured. The primary outcome is the proportion of patients with PTS at 24 months.

Ethics and dissemination:

Based on current knowledge the standard application of ECS therapy is questioned. The IDEAL DVT study will address the central questions that remain unanswered: What individual patients do benefit from ECS therapy and what is the optimal individual treatment duration? Primary ethics approval was received from the Maastricht University Medical Centre.

Results of the study will be disseminated via peer-reviewed publications and presentations at scientific conferences.

Trial Registration number:

NCT01429714 and NTR 2597

Background

After deep vein thrombosis (DVT) 20-50% of patients develop post thrombotic syndrome (PTS). PTS is a chronic condition, characterized by leg complaints such as pain; heaviness; cramps; aching; tingling; and leg signs due to venous insufficiency, evolving in severe cases to venous ulceration of the leg that was affected by the DVT.¹⁻⁵ PTS is a serious affliction, with substantial impact on quality of life and costs.^{2,6} Because an effective therapy is lacking, prevention of PTS is of major importance.

Up till now, elastic compression stocking (ECS) therapy after DVT has been the mainstay of PTS prevention. The evidence sustaining the value of ECS therapy following acute DVT is derived from 2 randomized clinical trials, which showed that incidences of PTS were reduced by approximately 50%, with application of ECS therapy for 24 months.^{7,8} However, based on these trials it is still undecided whether all patients benefit to the same extent from ECS therapy or what the optimal duration of ECS therapy for individual patients should be. We have previously assessed the safety of shortened duration of ECS therapy based on individual patient clinical scores in a management study of 125 patients, and we have shown that tailoring the duration of ECS therapy based on the signs and symptoms of the individual patient after an initial treatment period of 6 months, is a safe strategy to prevent PTS. We found that 50% of our patients did not need ECS therapy for as long as 2 years, while the overall incidence of PTS was 21.1% (95% CI 13.5- 28.7).⁹ This incidence is comparable to published incidences after 24 months ECS therapy.^{7,8} While this was a prospective management cohort study with an open character and therefore prone to bias, the results of this study need to be confirmed by an adequately powered randomized controlled trial.

There have been other studies that highlighted different aspects of ECS therapy. ECS therapy may not be indicated for all patients as shown by a study that assessed whether ECS therapy initiated one year after the event of DVT would lower the incidence of PTS in patients without complaints but with reflux on duplex testing. No significant benefit of ECS therapy at this late time of onset was found. The incidence of PTS was low in both groups.¹⁰ One study so far assessed whether prolonged duration of ECS therapy was superior to 6 months of ECS therapy following an event of proximal DVT. In this study no significant difference in the incidence of PTS according to the CEAP classification was observed between the two treatment groups.¹¹

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7 The proposed IDEAL (individually tailored elastic compression against (=versus) longterm therapy)
8 DVT study is a non-inferiority trial and aims to demonstrate that the assessed alternative therapy
9 based on ECS for 6 months followed by individually prolonged ECS therapy based on Villalta scores is
10 non-inferior to the comparator ECS therapy for a standard duration of 24 months. In addition we are
11 interested to study the cost-effectiveness of individual tailoring of the duration of ECS therapy via a
12 cost-utility analysis (CUA) and we want to retrieve information on the patient's motivations for
13 compliance or non-compliance to therapy. Because compliance to therapy is one of the most
14 important prerequisites for successful ECS therapy, a discrete choice experiment (DCE) will be
15 performed in which patient preferences towards ECS therapy will be assessed, in order to reveal the
16 main obstacles for compliance to therapy. For this purpose, a DCE questionnaire will be send to a
17 subset of the population (300 patients) at approximately 3 months after DVT.

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24 The results of a recently published placebo controlled trial performed by Kahn et al. refuted the routine
25 wearing of ECS after DVT altogether.¹² This study showed no treatment effect at all from ECS therapy
26 in contrast to the large treatment effects found in previous non-placebo controlled trials.^{7 8} The
27 unexpected lack of effectiveness cannot be dismissed solely as a placebo effect. The compliance to
28 ECS therapy, a major determinant of effectiveness, was 55.6% after 24 months. This was less in
29 comparison to the previous trials by Brandjes and Prandoni, where compliance was up to 90%.^{7 8 12}
30 Although a per protocol analysis of the patients reporting regular stocking use yielded the same
31 outcome, this sub analysis may not be adequately powered to dismiss lack of compliance as an
32 important determinant of non-effectiveness.

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38 Based on current knowledge it is therefore understood that the standard application of ECS therapy is
39 questioned. Especially the benefit to individual patients and the optimal duration of ECS therapy were
40 never studied properly and as a result it is unclear which individual patients require therapy and for
41 how long.

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45 The IDEAL DVT study aims to address these topics. In addition quality of life, patient preference
46 towards ECS therapy, compliance to therapy, as well as cost-effectiveness of ECS therapy will be
47 assessed.

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50 The primary outcome of the IDEAL DVT study will be PTS at 24 months after the event. The
51 secondary outcomes will be: 1. Health Related Quality Of Life, measured by questionnaires (SF-36¹³,
52 EuroQOL-5D¹⁴, Dutch translated Veines-Qol¹⁵, 2. Costs¹⁶), 3. Recurrent thrombosis, according to
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7 criteria as published¹⁷ and assessed by objective tests, 4. VTE related death during follow-up,
8 assessed by an independent and blinded adjudication committee, 5. Patient preferences, assessed
9 with a Discrete Choice Experiment (DCE)¹⁸.
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12 The scope of the problem in the Netherlands

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14 In the Netherlands, each year around 25.000 patients experience a new event of DVT. In order to
15 prevent PTS, common practice is to prescribe custom fitted ECS therapy for 2 years for all patients.¹⁹
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17 ²⁰ ECS therapy is costly, demanding and sometimes even debilitating. Elderly patients can often not
18 apply the ECS by themselves but need help from family or they even need home care visits (7.5%).²¹⁻
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20 ²³ Total annual costs of ECS therapy roughly amounts to 2.5 million euro for stockings (25.000
21 patients*100 euro) and 21 million euro for home care (7.5%*25.000 patients*500 visits*20 euro).²¹⁻²³
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23 Moreover, the majority of patients do not experience any post thrombotic complaints.¹⁰ In the
24 Netherlands, over 10 million euro each year could be saved if ECS treatment would be individualized.
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29 **Methods/Design**

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31 A multicentre, single-blinded, allocation concealed, randomized, non-inferiority trial comparing
32 individually tailored duration of ECS therapy (intervention) with standard duration of 24 months ECS
33 therapy (control), for the prevention of PTS. Randomization will guarantee a balanced distribution of
34 patients within each patient group. Stratification will be performed on centre and potentially
35 confounding effects such as age, sex and body mass index. The study will be a multicenter study in
36 order to get a good representation of patients and to achieve sufficient patient numbers. The primary
37 outcome will be PTS at 24 months after the event; the observers will be blinded to the allocated
38 treatment arm. The allocation will be concealed from study personnel involved in assessing the leg
39 symptoms and rating the PTS scores. Both randomization and allocation concealment are used as
40 strategies against bias. The study is not double blinded; no inactive stockings will be used in the
41 comparator group. The use of sham stockings will very likely interfere with the quality of life and will
42 complicate the assessment of perceived differences between groups. Patients will be followed for the
43 entire study duration; incidence of recurrent DVT and VTE related death during the follow-up period
44 will be documented.
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7 Patients and treatment

8 Consecutive, consenting adults with an acute objectively documented proximal DVT of the leg,
9 adequately treated with anticoagulant treatment and initial compression therapy according to a
10 prespecified protocol are included in the study. Patients are included and randomized in the IDEAL
11 DVT study within 2-6 weeks after DVT.
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13 Exclusion criteria are:

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- 16 • Previous DVT in the affected leg. Patients with a previous ipsilateral DVT might already have
17 developed PTS after the first DVT.
 - 18 • Recurrent DVT in the 6 months following inclusion, as it cannot be justified to advise these
19 patients to discontinue ECS therapy 6 months after DVT.
 - 20 • Pre-existent venous insufficiency (skin signs C3-C6 on CEAP score or requiring ECS therapy).
21 Pre-existent venous insufficiency increases the risk of developing PTS and the majority of
22 patients with venous insufficiency already chronically wear elastic compression stockings. In
23 addition venous insufficiency is closely related to PTS and is therefore difficult to differentiate
24 from PTS.
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 - 26 • Contraindication for ECS therapy such as intermittent claudication or clinical signs of leg
27 ischemia or asymptomatic arterial insufficiency (a pulse deficit or bruit at sites of narrowing at
28 physical examination).
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 - 30 • Active thrombolysis, as thrombolysis reduces the risk of PTS.
 - 31 • Limited life expectancy (< 6 months), as the follow-up period is 2 years.
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39 Patients are recruited from 12 hospitals in the Netherlands and 2 hospitals in Italy.

40 There is a prespecified protocol for the management of DVT in all participating centres.

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42 In the initial acute phase after DVT, until the acute oedema has disappeared, one of three strategies
43 will be applied. The leg is either bandaged with short stretch bandages to a compression of 30-40
44 mmHg, worn day and night and redressed twice per week; or a bandage stocking with 35mmHg
45 compression is prescribed (Mediven Struva 35[®], Medi, Breda, the Netherlands), worn day and night;
46
47 or no initial compression therapy is applied, according to the prespecified strategy of the hospital
48 protocol. After the initial phase, a custom fitted, flat knitted, knee length graduated elastic compression
49 stocking class III (ankle pressure 40 mmHg) is prescribed for all patients. The same brand and type
50 (Mediven 550) of compression stocking is prescribed to all patients in all participating centres.
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Compression therapy with the elastic compression stocking is started immediately after the initial phase, so there is no period without compression in between, with exception of the patients who do not receive compression in the initial phase. Patients receive two new stockings every year. Patients are advised to wear the stockings during the daytime.

Procedures

After obtaining written informed consent, randomization is performed centrally at the coordinating study centre, the Maastricht University Medical centre. Patients are included and randomized within 2-6 weeks after diagnosis of DVT. Patients are randomized to one of the two treatment arms. (Figure 1)

A web-based randomisation program (TENALEA (Trans European Network for Clinical Trials Services)) is used that executes blocked randomisation with stratification on centre-level and on possible confounding patient characteristics such as age, sex, and Body Mass Index ($<26 \text{ kg/m}^2$ - $\geq 26 \text{ kg/m}^2$). Permuted blocks of randomly varying size are used to maintain balance of numbers in each treatment group and to ensure allocation concealment.

Information on allocation is only accessible to the study personnel at the coordinating study centre in Maastricht, and patients will receive information about their allocation via the coordinating study centre. The allocation will be concealed from study personnel involved in assessing the leg symptoms and rating the PTS scores. Patients are not blinded by the use of sham stockings, because they may influence quality of life, complicating the assessment of perceived differences between groups. Patients are asked not to reveal their treatment allocation to their own physician, and not to wear the elastic compression stocking at the day of their outpatient clinic visits.

All patients are advised to wear the elastic compression stocking during the first 6 months after DVT. In the control group, all patients are instructed to wear the elastic compression stocking daily for a total duration of 2 years. In the Intervention group, duration of ECS therapy is individually tailored based on Villalta scores.²⁴ After the first 6 months therefore, there are three scenarios:

- (1) The Villalta score at both the 3 and 6-month follow-up visit is ≤ 4 . Then the patient is advised to discontinue ECS therapy.
- (2) The Villalta score at the 3-month follow-up visit is ≥ 5 the Villalta score at the 6 month follow-up visit is ≤ 4 . The patient is advised to continue the ECS therapy for another 6 months. If the

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7 Villalta score at the 12 month follow-up visit is ≤ 4 , the patient is allowed to discontinue the
8 ECS therapy.

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10 (3) The Villalta score is ≥ 5 at both the 3 and 6 months follow-up visit. The patient is advised to
11 continue the ECS therapy for a total duration of 24 months. (Figure 2)
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15 Using this algorithm the duration of ECS therapy is individually tailored in each patient. The decision
16 on the duration of ECS therapy in patients in the intervention group is made centrally at the
17 coordinating study centre, as only there the information on treatment allocation is available. The
18 patient is informed about the decisions on the (dis) continuation of the ECS therapy by the
19 coordinating centre.
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22 When a patient develops symptoms and signs of PTS after discontinuation of ECS therapy, a
23 predefined protocol is followed. If necessary, ECS treatment will be reinstated.
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27 Follow-up

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29 All patients are followed for 24 months after DVT. During these 24 months they visit the outpatient
30 clinic 4 times: at 3, 6, 12, and 24 months after the DVT. At each follow-up visit the signs of PTS will be
31 recorded and scored, by the study nurse or the treating physician, using the objective part of the
32 Villalta clinical scale for PTS.²⁴ In case of intermittent leg complaints or signs or symptoms suspect of
33 recurrent VTE, patients are instructed to visit their treating physician. Study documentation will be
34 filled out and adverse events will be recorded. The CCMO (central committee human related research)
35 will be notified in case of serious adverse events or death.
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41 The patient is asked to fill out 5 questionnaires: at baseline, and 3, 6, 12 and 24 months later. All
42 questionnaires will be offered as a web based application, each patient will have a unique personal
43 entry code. For patients who are not able or willing to use the electronic questionnaires, a paper
44 version will be available. The first questionnaire is filled out shortly after inclusion (4-6 weeks after
45 DVT) and the subsequent questionnaires are filled out the day before each follow-up visit. All
46 questionnaires contain the subjective part of the Villalta clinical scale for PTS²⁴, questions on ECS
47 compliance, a cost questionnaire¹⁶, and three health related quality of life (HRQOL) questionnaires:
48 the Dutch translated Veines-Qol¹⁵, the SF-36¹³, and the EuroQOL-5D¹⁴. In a subset of the study
49 population patient preferences regarding elastic compression therapy will be analysed, by conducting
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7 a discrete choice experiment (DCE). For this purpose, a DCE questionnaire will be sent to a subset of
8 the population at approximately 3 months after DVT.
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10 Compliance to ECS therapy is monitored in two ways. Each questionnaire contains a question on
11 compliance to the advised version of ECS therapy. Because compliance and adherence to therapy is
12 of crucial importance the number of contact moments for the assessment of compliance with ECS
13 therapy will be increased by adding telephone contacts to the regular clinical visits. Study-supporting
14 staff will make computer-assisted random telephone calls during the entire follow-up period to both the
15 patients in the group with the 2-year ECS intervention and to patients in the group with individualized
16 ECS therapy. The telephone calls will be made randomly to create a surprise effect (patients are off
17 guard) and to allow for a distribution of contacts over the entire study period. Per patient 3 extra
18 contact moments will be created. A standard questionnaire will be used to assess compliance and to
19 address reasons for non-compliance. Crossover to another therapy arm will be discussed and
20 discouraged.
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30 Outcomes

31 The primary outcome is the proportion of patients with PTS at the end of follow-up, 24 months after
32 DVT. PTS is defined as a Villalta score of ≥ 5 at two consecutive visits that are at least three months
33 apart. The time point of the second Villalta score of ≥ 5 will be considered the time point of PTS
34 diagnosis. Although the consensus is to diagnose PTS at the 6-month visit or later based on one
35 single Villalta score ≥ 5 ²⁵, we modelled this study after the preceding management study in which two
36 consecutive Villalta scores ≥ 5 were needed for the diagnosis PTS. We observed that a proportion of
37 patients (about 12%) had fluctuating Villalta scores beyond 6 months after the acute event of DVT.⁹
38 Assigning the diagnosis based on one single score ≥ 5 would therefore lead to misclassification and
39 overestimation of the PTS incidence. The Villalta scores at 6 months will be available; therefore also
40 the proportion of patients with PTS according to the consensus scoring method will be presented.
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49 Secondary outcomes include:

- 50 1. HRQOL, measured by questionnaires (SF-36¹³, EuroQOL-5D¹⁴, Dutch translated Veines-QoL¹⁵), 2.
- 51 Costs¹⁶, 3. Recurrent thrombosis, according to criteria as published¹⁷ and assessed by objective
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7 tests, 4. VTE related death during follow-up, assessed by an independent and blinded adjudication
8 committee, 5. Patient preferences, assessed with a Discrete Choice Experiment (DCE)¹⁸.
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11 Since both effects on costs and generic health-related quality of life are to be expected, the method of
12 economic evaluation is a cost-utility analysis (CUA). The analysis will be from a societal perspective.
13 The primary effect parameter is generic health-related quality of life, measured in quality adjusted life
14 years (QALYs). We will perform two analyses: a trial based CUA with a time horizon of two years
15 (identical to the duration of follow up in the clinical study), and a model-based CUA with a lifelong time
16 horizon. For the latter, we will follow the guidelines of good modelling.²⁶ We will be able to adapt a
17 Markov model for diagnostic strategies in DVT, which was developed by our group earlier.²⁷ Costs in
18 the economic analyses include direct health care costs (medical costs for prevention, diagnostics,
19 therapy, rehabilitation and care), direct non-health care costs (travel costs) and indirect costs
20 (productivity loss). Utilities will be calculated from the responses on the EQ-5D and SF36 classification
21 systems using the available multi-attribute utility functions.^{28 29} Incremental cost-utility ratios will be
22 calculated, and non-parametric bootstrap analyses will be used to quantify the uncertainty surrounding
23 the cost-utility ratio of the trial-based analysis. Sensitivity analyses and subgroup analyses will be
24 performed, to assess the impact of variation in parameters and heterogeneity of the patient population.
25 ECS therapy has several disadvantages for the patients (stockings are uncomfortable, ugly, and
26 difficult to put on and off), while duration and effectiveness are uncertain. A DCE will be conducted to
27 assess the patient preferences regarding ECS therapy, providing insight in the trade-offs patients
28 make between characteristics of the therapy when deciding to wear the stocking or not. Duration of
29 ECS therapy is one of the characteristics. Data will be analysed using multinomial logit models and
30 mixed logit models. (Nlogit, Econometric Software)
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45 Sample size calculation

46 The proposed study is a non-inferiority trial and aims to demonstrate that the assessed alternative
47 therapy based on ECS for 6 months followed by individually prolonged ECS therapy based on Villalta
48 scores is not worse than the comparator ECS therapy for a standard duration of 24 months, by more
49 than the prespecified amount of 7.5% (the non-inferiority margin). The published incidence of PTS
50 following two years of ECS lies between 20 and 30%. (Prandoni 24.5% (95% CI 15.6- 33.4), Brandjes
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7 20% (95% CI 12.4-29.2)^{7 8} As it is statistically impossible to demonstrate equivalence (prove the H0 of
8 no difference), Blackwelder proposed a one sided significance test to reject the null hypothesis by a
9 clinically acceptable amount.³⁰ If we allow a difference of 7.5% in the outcome PTS between the group
10 with ECS for 2 years and the group with the alternative therapy, 70% of the effect will be preserved.
11 This proportion of loss in efficacy is customarily accepted in controlled randomized clinical trials. At a
12 one sided significance level of 0.05 and a power of 80%, with a ratio of 1, a total of 847 patients is
13 needed to provide sufficient patients for an adequately powered trial.^{30 31} Loss to follow-up of patients
14 is expected to be less than 2% since the intervention does not have an invasive nature. Therefore, a
15 total of 864 patients are needed (432 patients per treatment arm).
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22 Statistical analysis

23 Descriptive statistics of the total population and of the two treatment groups separately will be
24 computed to provide baseline characteristics of the patients in both treatment arms.
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26 For the primary outcome PTS, univariate analysis of all proportions will be performed with logistic
27 regression (chi-squared) analysis. Kaplan-Meier method will be used to calculate the cumulative
28 incidences of PTS, adjusted for centre, to compare incidence rates between the two treatment arms.
29 Patients who die or are lost to follow-up will be censored at their last visit. ANOVA will be applied to
30 assess changes over time, by comparing different outcome measures at the different time points of
31 follow-up.
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33 Hazard ratio's and 95% confidence intervals for both treatment arms will be calculated using Cox
34 regression models. Hazard ratio's will be stratified for centre and adjusted for age, sex, BMI, clinical
35 presentation of DVT, and extent of the index deep vein thrombosis.
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38 Interim analysis (safety)

39 A prespecified safety analysis will be performed when 50% of the subjects have completed the 2-year
40 follow-up. The analysis will be performed by the coordinating centre, and supervised by the principal
41 investigators. The safety analysis will be performed to assess significant enhanced risk of PTS or
42 excess morbidity/mortality in the intervention arm of the study population. Fisher's exact test will be
43 performed to compare incidence of PTS at a significance level of 0.05 (two sided). The study can
44 be stopped in case of significant excess morbidity/mortality in the alternative treatment arm.
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Ethical considerations

The medical ethical committees of all participating hospitals in the Netherlands and Italy approved this study. All patients are extensively informed about the study, and written informed consent is obtained from all participating patients.

The IDEAL DVT study started including patients at 11th of March 2011 and inclusion is currently on-going. Recruitment is expected to be terminated in January 2015. As the follow-up is 2 years, the results are expected within 3 years, in January 2017.

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Discussion

Based on current knowledge the standard application of ECS therapy after DVT is questioned. The definitive answer on the usefulness of ECS therapy for the prevention of PTS is not yet provided. Therefore the need for the IDEAL DVT study remains unchanged. The benefit to individual patients and the optimal duration of ECS therapy were never studied properly and as a result it is unclear which individual patients require therapy and for how long. The IDEAL DVT study will address the central questions that remain unanswered: What individual patients do benefit from ECS therapy and what is the optimal individual treatment duration? The study that we plan to perform is not only innovative; for the first time individual tailoring of duration of ECS therapy will be investigated, but also it will provide unique additional knowledge on the safety, effectiveness and cost-effectiveness of this approach. ~~The IDEAL DVT study started including patients March 2011 and is currently on-going. Recruitment is expected to be terminated within 1 year. As the follow-up is 2 years, the results are expected within 3 years.~~

Trial status

The IDEAL DVT study is currently in progress. Patient recruitment started March 15th 2011 and is still on-going.

Acknowledgments

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We especially acknowledge the participating investigators.

Competing interests

The authors declare that they have no competing interests.

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Contributions

AtC wrote the protocol and designed the study, the other authors MJ (cost-effectiveness research), MP (study design/statistics) and HtC (study design) contributed. AB is a PhD student and coordinator of the trial.

Ethics approval

Maastricht University Medical Centre.

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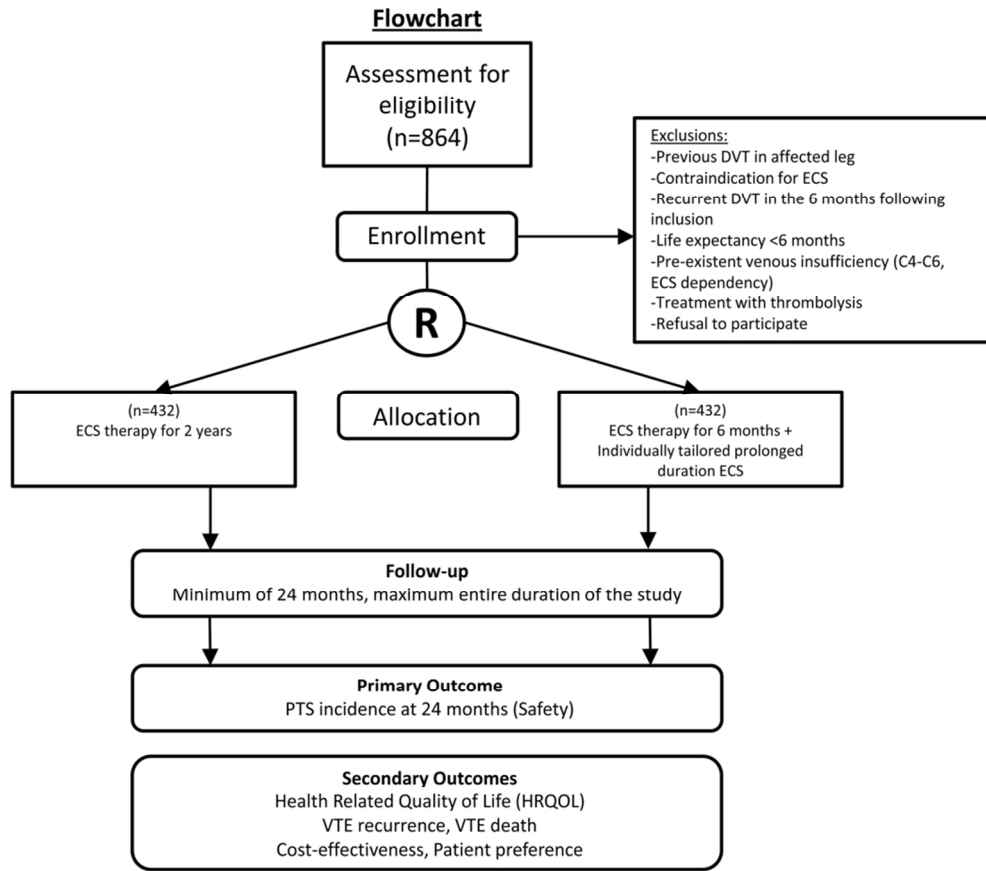


Figure 1. Study flow diagram
90x79mm (300 x 300 DPI)

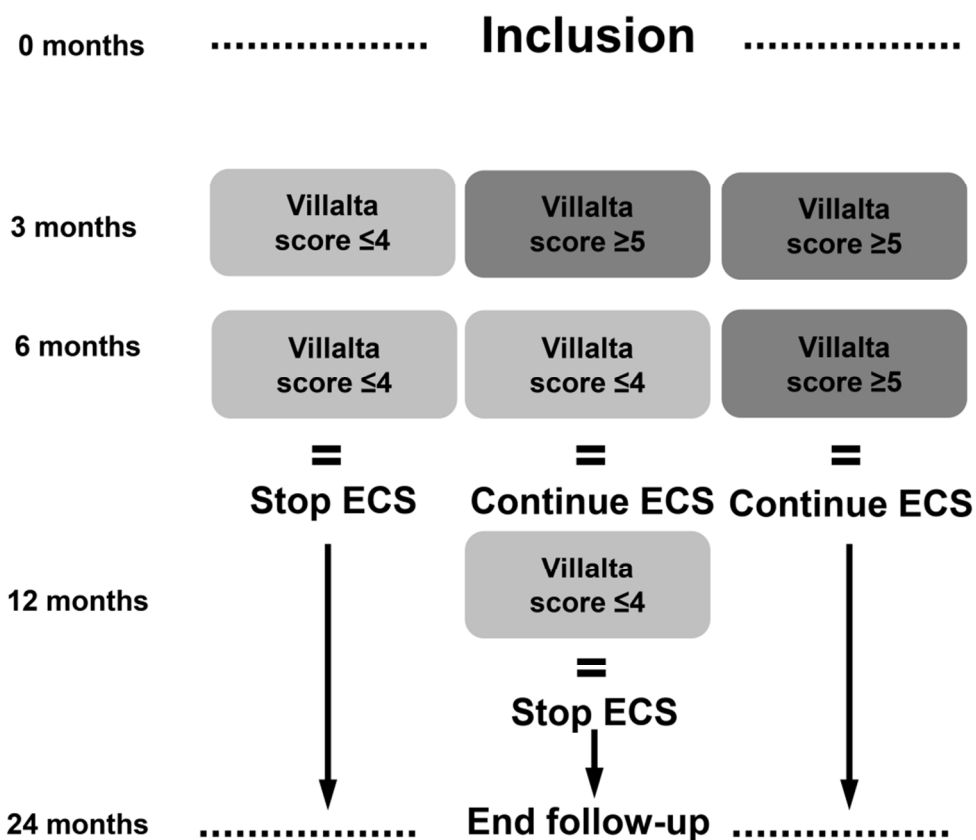


Figure 2. Algorithm individually tailored ECS therapy
90x77mm (300 x 300 DPI)