Individually shortened duration versus standard duration of elastic compression therapy for prevention of post-thrombotic syndrome: a cost-effectiveness analysis

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Summary

Background The IDEAL DVT study showed that it was safe to shorten the duration of elastic compression therapy on an individualised basis after deep vein thrombosis for prevention of post-thrombotic syndrome. In this study, we assessed the cost-effectiveness of this strategy.

Methods IDEAL DVT was a multicentre, randomised, non-inferiority trial that included patients with acute proximal deep vein thrombosis of the leg. After 6 months of elastic compression therapy, patients were randomly assigned (1:1) to the standard 2 years of elastic stocking compression therapy or shortened duration of compression therapy based on the patient's Villalta score. For our cost-effectiveness analysis, we assessed quality-adjusted life-years (QALYs), measured with the three-level version of EQ-5D (EQ-5D-3L; Dutch and UK tariff) and the 36-item Short Form Health Survey (SF-36), and costs in € (health-care and societal perspective) according to the intention-to-treat approach. Data were collected at 3, 6, 12, and 24 months after diagnosis of thrombosis. We calculated incremental net monetary benefit using a QALY threshold of €30 000, and obtained bootstrapped means and 95% CIs. IDEAL DVT is registered with ClinicalTrials.gov, number NCT01429714.

Findings Between March 22, 2011, and July 1, 2015, 865 patients were enrolled in IDEAL DVT. 437 were assigned to individualised duration of elastic compression therapy and 428 to standard duration of elastic compression therapy. Nine patients were eventually excluded because of recurrent venous thromboembolism within 6 months after the first event. From a societal perspective, for every QALY lost measured with the EQ-5D Dutch tariff, cost savings were €305·992 (incremental net monetary benefit €3205, 95% CI 502–5741), and for every QALY lost based on the Short-Form Six-Dimension (SF-6D) utility score (derived from SF-36), cost savings were €6030·941 (€3540, 95% CI 1174–5953). Using the UK tariff for EQ-5D, the individualised strategy was more effective and less costly (€4071, 1452–6647). The probability that the individualised strategy was cost-effective was 99% at a threshold of €30 000 per QALY (EQ-5D Dutch tariff).

Interpretation Individually shortened duration of elastic compression therapy was cost-effective compared with standard duration elastic compression therapy. Use of an individualised approach to elastic stocking compression therapy for the prevention of post-thrombotic syndrome after deep vein thrombosis could lead to substantial costs savings without loss in health-related quality of life.

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Introduction

Post-thrombotic syndrome is a long-term consequence of deep vein thrombosis. 20–50% of patients diagnosed with deep vein thrombosis develop post-thrombotic syndrome within 2 years after diagnosis of a deep vein thrombus in the leg.[1] The syndrome is irreversible and characterised by oedema, skin changes—which can range from mild skin signs to venous ulcers—and leg complaints.[2,3] Post-thrombotic syndrome is associated with disability and decreased quality of life. As severity increases, quality of life worsens.[4] Furthermore, post-thrombotic syndrome is associated with substantial economic costs.[5,6]

To prevent post-thrombotic syndrome, all patients with thrombosis of the leg are advised to wear elastic compression stockings for 2 years.[7–9] A Cochrane meta-analysis[10] found that compression therapy caused a 30% reduction in the occurrence of post-thrombotic syndrome. However, costs of the use of elastic compression stockings are not negligible. In the Netherlands alone, the cost of stockings for prevention of post-thrombotic syndrome was estimated to be €2·5 million per year.[11] Not all patients can apply and remove the stockings independently; in the Netherlands, €21 million is needed for home care to assist patients with the application of stockings.[12–14] Hence, if the duration of elastic compression

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Research in context

Evidence before this study

We did a systematic literature review in April, 2018. We searched MEDLINE, the Current Controlled Trials database, the UK National Health Service Centre for Reviews and Dissemination database, and the Health Economic Evaluation database for any type of article, with no date or language restrictions, using the search terms ("post thrombotic syndrome" OR "post phlebitic syndrome") AND "compression therapy" AND "cost". When including the term "cost" we found no results. When excluding the term "cost", we found two studies that reported on variable duration of compression therapy. One trial from 2008 compared treatment with 6 months of elastic compression therapy with a prolonged duration of 24 months and showed no difference between groups in post-thrombotic skin changes assessed according to the Clinical, Etiological, Anatomical, Pathophysiologic score. The OCTAVIA study compared standard 24 months of elastic compression therapy with 1 year of compression therapy in selected patients with Villalta scores of less than 5 and excellent adherence to compression therapy, and did not show non-inferiority for the shortened duration of therapy. In December, 2017, we reported the primary outcome of the IDEAL DVT study showing that individualised shortened duration of elastic compression therapy for prevention of post-thrombotic syndrome was feasible and was not associated with significant differences between groups in the proportion of patients with post-thrombotic syndrome after 2 years. We concluded that individualised duration of elastic compression therapy was safe and effective and was likely to reduce health-care costs.

Added value of this study

To our knowledge, this analysis of IDEAL DVT is the first to assess the cost-effectiveness of an individualised shortened duration of elastic compression therapy compared with standard 2-year duration. We found the individualised strategy to be cost-effective. Because most patients who develop post-thrombotic syndrome are diagnosed in the first 2 years after diagnosis of deep vein thrombosis, we assumed that this timeframe would be sufficient to capture the most important differences in costs and health effects. In a subgroup analysis we assessed the cost-effectiveness of shortened duration of elastic compression therapy in a subset of patients with low Villalta scores (<5) at 6 months compared with a similar selection of patients within the standard treatment group. We found that despite slightly more occurrences of post-thrombotic syndrome in the group with individualised shortened treatment duration, for this subgroup of patients the individualised strategy was cost-effective.

Implications of all the available evidence

We showed that by using an individualised approach, substantial cost savings can be made, both from a health-care perspective and a societal perspective, without significant loss in health-related quality of life. Therefore, individualised compression therapy should be embedded in current guidelines and implemented in daily practice.

stocking treatment could be shortened in patients for whom it is safe to do so, a substantial burden to patients and society could be saved.

The IDEAL DVT study[15] investigated individualised versus standard duration of elastic compression therapy for prevention of post-thrombotic syndrome. Most patients in the individualised group were able to stop treatment early; 236 (55%) of 432 patients wore the stockings for only 6 months. No significant difference between groups was reported in the proportion of patients with post-thrombotic syndrome at 24 months (odds ratio 1·06, 95% CI 0·78–1·44). However, a post-hoc analysis of 420 patients without symptoms at 1 year after diagnosis of thrombosis and with excellent adherence to therapy showed increased incidence of mild post-thrombotic syndrome in patients who stopped stocking treatment early on the basis of the International Society on Thrombosis scoring method for the Villalta score (risk ratio 1·6, 95% CI 1·2–2·3).

To our knowledge, only two other studies have assessed variable duration of elastic compression therapy to prevent post-thrombotic syndrome,[16,17] but neither assessed the cost-effectiveness of such strategies.

We report a health economic evaluation of the IDEAL DVT study. We assessed the cost-effectiveness of individualised duration of elastic compression therapy compared with standard duration, both from a health-care perspective and from a societal perspective. Additionally, we assessed whether it was cost-effective to provide patients with mild post-thrombotic syndrome—as identified by a post-hoc analysis—with prolonged compression therapy.

Methods

Study design and participants in IDEAL DVT

The IDEAL DVT study, a multicentre, randomised, single-blind, allocation-concealed, non-inferiority trial, was done at 12 hospitals in the Netherlands and two hospitals in Italy.[15] Patients with acute proximal deep vein thrombosis of the leg, without pre-existing venous insufficiency (Clinical Etiological Anatomical and Pathophysiologic [CEAP] score <C3), were randomly assigned (1:1) to individualised duration of elastic compression therapy or to standard duration compression therapy for 2 years. Randomisation was done with a web-based automatic randomisation programme (TENALEA) with a random block size (2–12), and was stratified by centre, age, and body-mass index. All patients wore elastic compression stockings for the first 6 months after diagnosis of deep vein thrombosis. After 6 months, the duration of further use of elastic compression stockings in patients in the

individualised treatment group depended on the patient's signs and symptoms assessed with the Villalta score. Patients who were assigned to standard duration of stocking therapy were instructed to wear elastic compression stockings for the entire 2-year duration of the study. Follow-up visits in the study were at 3, 6, 12, and 24 months after diagnosis of deep vein thrombosis. 865 patients were enrolled between March 22, 2011, and July 1, 2015; 437 were assigned to individualised duration and 428 to standard duration of treatment.[15] The primary endpoint of IDEAL DVT was post-thrombotic syndrome at 24 months. IDEAL DVT is registered with ClinicalTrials.gov, number NCT01429714.

Data inputs

For our cost-effectiveness analysis, we used data on utilities (health-related quality of life weights), resource use, and productivity from the IDEAL DVT trial.[11] In the trial,[11] at a one-sided significance level of 5% and a power of 80%, a sample size of 848 was required to test the hypothesis on the basis of an expected incidence of post-thrombotic syndrome of 20–30%. Loss to follow-up was expected to be less than 2%, thus a sample of 864 was needed. Costs and utilities were collected prospectively for every patient at 3, 6, 12, and 24 months after diagnosis of acute deep vein thrombosis. In cases of recurrent ipsilateral thrombosis within the first 6 months after diagnosis, patients were excluded from further assessment.

Utilities were measured with the three-level version of EQ-5D (EQ-5D-3L) and the 36-item Short Form Health Survey (SF-36) version 2.[18–20] Patients received a link by email to an online questionnaire. Patients that did not have internet received a paper version via mail. The questionnaires were completed the day before the clinic visit. EQ-5D-3L is made up of five questions with three options (no, moderate, or severe problems) regarding five dimensions of general health status (mobility, self-care, usual activity, pain, and anxiety). For calculation of utilities from EQ-5D-3L scores, we used both the Dutch tariff and the UK tariff.[21,22] SF-36 consists of 36 questions regarding the health domains of physical functioning, physical role functioning, emotional role functioning, social role functioning, mental health, bodily pain, vitality, and general health perceptions. From SF-36 scores, we derived the Short-Form Six-Dimension (SF-6D) utility score.[23]

For the purposes of this study we developed a cost questionnaire containing items to assess use of health-care resources (general practitioner, medical specialist, anticoagulation clinic, physiotherapist, need for home care, use of elastic compression stockings, and medication use), patient costs (travel costs to medical facilities), and indirect costs (work productivity loss) related to leg complaints. For work productivity loss, we applied the prospective modular Productivity and Disease Questionnaire.[24] This questionnaire used a recall period of 3 months. The guideline on health economic evaluation drafted by the Netherlands Health Care Institute was used for the standard unit price for the items in each cost category.[25] We calculated the costs related to work productivity loss using the friction cost method as recommended in the Netherlands.[26] The friction cost method takes the employer's perspective and only counts the costs of work productivity lost until another employee takes over the patient's work, assuming that long-term absentees are replaced.[26] The current friction period is set to 12 weeks in the Dutch health economic guideline.[25] All reported costs were in € at 2015 price levels.

Economic evaluation

The outcome for the economic evaluation was quality-adjusted life-years (QALYs). A QALY combines mortality and quality of life into a single index, multiplying time by utility. 1 QALY represents 1 life-year in perfect health. Hence, in this analysis a patient could experience a maximum of 2 QALYs. We derived QALYs from utilities on the basis of EQ-5D-3L (Dutch and UK tariffs) and SF-6D scores. Because the intervention only started at 6 months after enrolment of each patient, we used the group average (ie, mean) for the calculation of QALY in the first 6 months. After 6 months, we assumed for each patient that the utility between two consecutive measurements would equal the mean of those two measurements.

Because the cost questionnaire had a 3-month recall period, we interpolated the costs. Similar to the analysis of QALYs, we also used the group mean for the costs in the first 6 months for each patient. Subsequently, for each patient, we multiplied the costs reported at 12 months by 2 and the mean of the costs reported at 12 and 24 months by 4. We calculated health-care costs and societal costs. Societal costs consist of health-care and patient and family costs, and costs associated with lost productivity.

We determined cost-effectiveness by relating the incremental costs to the incremental QALYs over the 2-year time horizon. Additionally, we calculated incremental net monetary benefits by multiplying incremental QALYs by the customary threshold of €30 000 and subtracting the incremental costs. A positive incremental net monetary benefit indicates cost-effectiveness.

Ethics approval

Ethics approval was obtained from the institutional review board of Maastricht University Medical Centre (Maastricht, Netherlands; number 32073.068.10) and was ratified by the ethical review board of the participating centres. All participants gave written informed consent before any study-related activity was done.

Statistical analysis

We used the intention-to-treat approach for data analysis. We imputed missing data with single stochastic regression imputation, using chained equations to

prevent loss of statistical power and to decrease the probability of obtaining biased estimates. We assumed data were missing at random (ie, missing conditional on other covariates). We used predictive mean matching to draw the imputed values, because this method is more robust to misspecification of the imputation model and non-normality of continuous variables compared with standard regression imputation.[27] We assessed group comparability for differences in demographic and clinical characteristics, both for differences in QALYs and for costs. We assessed differences in demographic and clinical characteristics with an independent sample *t* test or Mann-Whitney *U* test depending on the normality of data distribution, and for categorical variables we used χ^2. We tested differences in quality of life over time with split plot ANOVA analysis. We used bootstrapping to obtain 95% CIs for QALYs, costs, and incremental net monetary benefits. In this method, cost and effectiveness (QALYs) pairs are randomly drawn from the original data with replacement until the size of the original sample is achieved. We drew 5000 bootstrap samples to obtain a stable result. We presented the results of the bootstrap simulation in a cost-effectiveness plane in which the incremental costs were plotted against incremental QALYs. We obtained CIs based on the 2·5th and 97·5th percentiles. We obtained cost-effectiveness acceptability curves to determine the probability of cost-effectiveness for individualised duration of elastic compression stockings versus standard duration of stockings for different thresholds for a QALY. Because the study predominantly investigated Dutch patients, we considered analysis with the QALY based on the EQ-5D-3L Dutch tariff as the base case. We did sensitivity analyses with QALYs based on the more widely used EQ-5D-3L UK tariff (to increase generalisability of our results and hence usefulness for other countries) and the SF-6D.

We did two additional analyses: a sensitivity analysis with complete cases (ie, without missing data), and a subgroup analysis in a subset of patients with low Villalta scores who stopped treatment at 6 months compared with patients with similar Villalta scores within the standard treatment group who continued stocking therapy until the end of study.

Analyses were done in SPSS version 23 and Excel version 10.

	Individualised duration of compression stocking use (n=432)	Standard 2-year duration of compression stocking use (n=424)	p value
EQ-5D Dutch tariff	..	..	0·26
3 months	0·8717 (0·2063)	0·8739 (0·1986)	..
6 months	0·8903 (0·1932)	0·8852 (0·1774)	..
12 months	0·8720 (0·2319)	0·8752 (0·2069)	..
24 months	0·8640 (0·2691)	0·8848 (0·1974)	..
EQ-5D UK tariff	..	..	0·36
3 months	0·8524 (0·2220)	0·8541 (0·2235)	..
6 months	0·8873 (0·1839)	0·8658 (0·1995)	..
12 months	0·8748 (0·2060)	0·8639 (0·2182)	..
24 months	0·8877 (0·2191)	0·8809 (0·1936)	..
SF-6D	..	..	0·38
3 months	0·6258 (0·0560)	0·6295 (0·0552)	..
6 months	0·7963 (0·1252)	0·7887 (0·1279)	..
12 months	0·8055 (0·1268)	0·8093 (0·1266)	..
24 months	0·8093 (0·1326)	0·8082 (0·1355)	..
QALYs over 2 years' time horizon			
Based on EQ-5D Dutch tariff	1·7487 (0·3223)	1·7602 (0·2509)	0·38
Based on EQ-5D UK tariff	1·7543 (0·2746)	1·7373 (0·2651)	0·51
Based on SF-6D	1·5628 (0·1747)	1·5633 (0·1773)	0·22

Data are mean (SD). QALY=quality-adjusted life-year. SF-6D=Short-Form Six-Dimension.

***Table 1*: Utilities and QALYs**

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and AJtC-H and MAJ had final responsibility for the decision to submit for publication.

Results

Between March 22, 2011, and July 1, 2015, 865 patients were enrolled in the study. 437 were randomly assigned to individualised duration of elastic compression therapy and 428 to standard duration of elastic compression therapy. Nine patients were eventually excluded because of recurrent venous thromboembolism within 6 months after the first event. Before imputation, the proportion of missing EQ-5D questionnaires was 68 (8%) of 856 at 3 months, 95 (11%) of 856 at 6 months, 134 (16%) of 856 at 12 months, and 198 (23%) of 856 at 24 months. For the SF-6D and cost questionnaires, these proportions were 139 (16%) of 856 at 3 months, 154 (18%) of 856 at 6 months, 194 (23%) of 856 at 12 months, and 259 (30%) of 856 at 24 months.

We found no statistically significant differences between the group utilities at any timepoint (table 1). QALYs based on the EQ-5D-3L Dutch tariff were 1·7487 (SD 0·3223, 95% CI 1·7177–1·7778) for individualised duration of therapy and 1·7602 (0·2509, 1·7355–1·7831) for standard duration of therapy. With the SF-6D, QALYs were 1·5628 (0·1747, 1·5458–1·5788) for individualised duration of therapy and 1·5633 (0·1773, 1·5462–1·5801) for standard duration of therapy. QALYs based on the EQ-5D-3L UK tariff were 1·7543 (0·2746, 1·7273–1·7790) for individualised duration of therapy and 1·7373 (0·2651, 1·7110–1·7619) for standard duration of therapy.

The mean societal costs were lower for individualised duration of compression therapy (€8251, 95% CI 6690 to 9690) compared with standard duration of therapy (€11 803, 10 020 to 13 651; table 2). The incremental societal costs amounted to –€3552 (95% CI –5793 to –1241; table 2). In both the individualised duration of

	Individualised duration of stocking use (n=432)			Standard 2 year duration of stocking use (n=424)			Incremental health-care cost, €	Incremental patient, family, and indirect cost, €	Incremental total societal cost, €
	Mean health-care cost, €	Mean patient, family, and indirect cost, €	Mean total societal cost, €	Mean health-care cost, €	Mean patient, family, and indirect cost, €	Mean total societal cost, €			
Visit									
3 months	1203	901	2108	926	997	1926	277	−96	182
6 months	602	705	1307	954	547	1501	−352	158	−194
12 months	671	199	870	1765	253	2018	−1094	−55	−1148
24 months	1213	227	1440	887	29	916	326	198	524
Total overall costs over 2 years	6027	2233	8259	9754	2042	11796	−3727	191	−3536
Total overall costs over 2 years, bootstrapped mean (95% CI)	6022 (5003 to 7061)	2245 (1465 to 3235)	8251 (6990 to 9690)	9740 (8054 to 11561)	2052 (1582 to 2575)	11803 (10020 to 13651)	−3718 (−5802 to −1740)	193 (−757 to 1242)	−3552 (−5793 to −1241)

Table 2: **Health-care, patient, family, and indirect costs**

therapy and the standard duration of therapy groups, the mean societal costs mainly consisted of health-care costs (€6022 [95% CI 5003 to 7061] for individualised duration, and €9740 [8054 to 11561] for standard duration; table 3). Health-care costs were mostly for home care (€4417·01 for individualised duration and €7438·60 for standard duration; table 3). Patient and family and productivity costs were slightly lower for individualised duration of stockings as compared with standard duration (€563 [95% CI 426 to 779] *vs* €601 [485 to 749]; table 3).

The mean incremental cost-effectiveness ratio in the base case equalled €305·992 saved per QALY lost with the EQ-5D-3L Dutch tariff (table 4). When QALYs were based on the SF-6D, the mean incremental cost-effectiveness ratio was €6030·941 saved per QALY lost (table 4). With the EQ-5D-3L UK tariff, the intervention was found to be more effective and cost saving (table 4). The incremental net monetary benefit in the base case was €3205 (95% CI 502–5741) with the EQ-5D-3L Dutch tariff, €4071 (1452–6647) with the EQ-5D-3L UK tariff, and €3540 (1174–5953) with SF-6D. The uncertainty surrounding the incremental costs and QALYs is shown in figure 1. The probability for the individualised strategy to be cost-effective was 99% at a threshold of €30 000 per QALY (on the basis of the EQ-5D-3L Dutch tariff; figure 2). The probability that the study was cost-effective at thresholds between €7000 and €82 000 was 90% at the lowest (figure 2). Complete case analysis showed that individualised shortened duration of compression therapy was more effective and cost saving compared with standard duration of compression therapy, irrespective of the instrument used to assess utilities for QALYs.

We compared the cost-effectiveness of shortened duration of therapy in the individualised intervention group for a subgroup patients who did not wear elastic compression stockings after 6 months compared with patients in the standard duration group who had similar Villalta scores and continued wearing the stockings until the end of the study. Although there was a slightly larger difference in post-thrombotic syndrome between these subgroups than between the entire individualised treatment group compared with the entire standard treatment group, we found slightly more cost savings for the individualised treatment subgroup (€3850 compared

	Unit cost, €	Individualised duration of stocking use (n=432)		Standard 2-year duration of stocking use (n=424)	
		Number of users	Mean cost, €	Number of users	Mean cost, €
Health-care costs					
General practitioner	33–50	94	188·27	107	200·66
General practitioner out of hours care	33–50	13	36·87	13	76·03
Medical specialist	91	139	494·85	145	537·70
Medication use	1·07–74·78	432	92·55	424	150·12
Anticoagulation clinic	9	316	178·93	299	227·60
Elastic compression stockings*	50	432*	127·30	424	339·28
Physiotherapy	33–50	50	491·30	48	783·87
Home care	23–73	76	4417·01	62	7438·60
Total health-care costs bootstrapped mean (95% CI)	..	..	6022 (5003–7061)	..	9740 (8054–11561)
Patient and family costs					
Travel costs	2·66–43·14	55	88·03	55	80·53
Family care	14	74	476·94	68	518·82
Total patient and family costs, bootstrapped mean (95% CI)	..	..	563 (426–779)	..	601 (485–749)
Indirect costs					
Productivity loss	34·75	34	1667·65	35	1442·90
Total societal costs					
Total societal costs, bootstrapped mean (95% CI)	..	..	8251 (6990–9690)	..	11803 (10020–13651)

*Difference in cost is due to difference in duration of wearing elastic compression stockings.

Table 3: **Total costs per category over 2 years**

	Incremental costs, €	Incremental QALY EQ-5D Dutch tariff	Incremental QALY EQ-5D UK tariff	Incremental QALY SF-6D	Incremental cost-effectiveness ratio [incremental net monetary benefit] with EQ-5D QALY Dutch tariff, €*	Incremental cost-effectiveness ratio [incremental net monetary benefit] with EQ-5D QALY UK tariff, €*	Incremental cost-effectiveness ratio [incremental net monetary benefit] with SF-6D QALY, €*
Base case†							
Observed mean	−3536	−0·0115	0·0170	−0·0004	..	..	..
Bootstrapped mean (95% CI)	−3552 (−5793 to −1241)	−0·0116 (−0·0506 to 0·0269)	0·0172 (−0·0194 to 0·0530)	−0·0006 (−0·0242 to 0·0229)	305·992 [3205] (502 to 5741)	Dominant [4071] (1452 to 6647)	6030·941 [3540] (1174 to 5953)
Complete cases							
Observed mean	−177	0·0167	0·0156	0·0091	..	..	..
Bootstrapped mean (95% CI)	−182 (−1055 to 715)	0·0167 (−0·0184 to 0·0458)	0·0150 (−0·0187 to 0·0490)	0·0093 (−0·0139 to 0·0330)	Dominant [683] (−745 to 2071)	Dominant [6323] (−910 to 2183)	Dominant [469] (−823 to 1746)
Post-hoc analysis: compression *vs* no compression for subgroup of patients with Villalta score ≤4 at 6 months							
Observed mean	−3850	0·0054	0·0330	0·0252	..	..	..
Bootstrapped mean (95% CI)	−3850 (−5811 to −1863)	0·0053 (−0·0329 to 0·0434)	0·0331 (−0·0051 to 0·0674)	0·0251 (0·0016 to 0·0480)	Dominant [4010] (1677 to 6305)	Dominant [4789] (2568 to 7085)	Dominant [4605] (2478 to 6772)

Dominant means that the strategy resulted in a better quality of life (effects) and more cost saving. SF-6D=Short-Form Six-Dimension. QALY=quality-adjusted life-years. *95% CIs in columns below are for the incremental net monetary benefit. †Base case refers to data of all patients with imputation of the missing values.

***Table 4*: Incremental cost-effectiveness results**

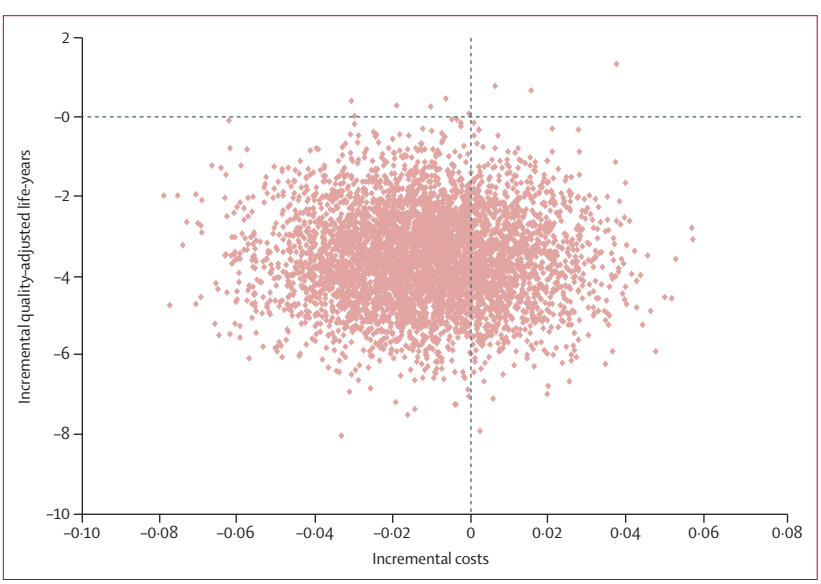

***Figure 1*: Bootstrapped incremental cost-effectiveness results (based on EQ-5D Dutch tariff) of individualised duration of elastic compression stocking treatment**

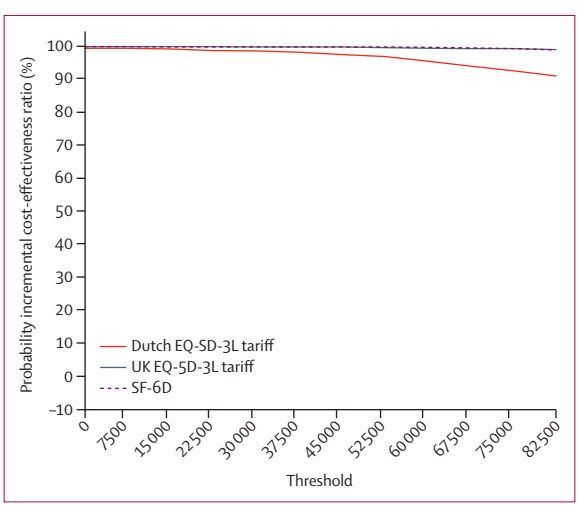

***Figure 2*: Cost-effectiveness acceptability curves of use of individualised duration of elastic compression stocking treatment versus standard duration of stocking treatment**
SF-6D=Short-Form Six-Dimension.

with €3536 for the entire population) and a gain in QALYs as compared with the overall population of patients in the IDEAL DVT trial.

Discussion

To our knowledge, this is the first health economic evaluation of the use of elastic compression therapy for prevention of post-thrombotic syndrome. We specifically directed our analysis at the cost-effectiveness of individualised shortened duration of therapy compared with standard duration of therapy, which is 2 years.[7–9]

Two previous studies have assessed variable duration of elastic compression therapy to prevent post-thrombotic syndrome,[16,17] but neither assessed the cost-effectiveness of such strategies. Aschwanden and colleagues compared 6 months of treatment with elastic compression therapy versus a prolonged duration of 24 months in patients with newly-diagnosed deep vein thrombosis.[16] They found that the occurrence of post-thrombotic skin changes, assessed according to the CEAP score, in the group allocated to 6 months of elastic compression therapy did not differ significantly from the group assigned to long-term duration of therapy (hazard ratio 0·60, 95% CI 0·28–1·28). In the OCTAVIA study,[17] selected patients with Villalta scores of less than 5 and excellent adherence to compression therapy were randomly assigned to standard 24 months of elastic compression therapy versus

1 year of compression therapy. This trial failed to show non-inferiority for the shortened duration of therapy: the absolute difference in occurrence of post-thrombotic syndrome was 6·9%, with the 95% CI upper limit of 12·3% exceeding the predefined non-inferiority margin of 10%. In December, 2017, we reported the primary outcome of the IDEAL DVT study,[15] which showed that individualised shortened duration of elastic compression therapy for prevention of post-thrombotic syndrome was feasible. We showed that 283 (66%) of 432 patients in the intervention group could stop treatment early, guided by a low Villalta score. We found no significant difference in the proportion of post-thrombotic syndrome after 2 years for those assigned to individualised shortened duration as compared with standard duration of therapy (odds ratio 1·06, 95% CI –0·78 to 1·44). We concluded that individualised duration of elastic compression therapy was safe and effective and anticipated that this treatment strategy was likely to reduce health-care costs.

Our results from this analysis show that quality of life as measured by EQ-5D-3L and SF-36 version 2 started increasing 3 months after the thrombotic event, and quality of life did not differ between patients assigned to individualised duration or standard 2-year duration of elastic compression therapy throughout the study. The costs for both treatment groups consisted mainly of health-care costs due to the high costs of home care. We found individualised duration of elastic compression therapy to be the most cost-effective option, irrespective of the instrument used to obtain utilities to calculate QALYs. In the Netherlands, for 25 000 incident cases of deep vein thrombosis per annum,[28] savings (measured over 2 years) from implementing the individualised strategy would amount to €88 million (95% CI 31 million to 144 million).

Sensitivity analysis with the complete cases showed individualised duration of elastic compression therapy was more effective and less costly than was treatment with standard duration of compression therapy. In the complete case analysis the cost savings were lower, but overall the individualised strategy was still cost-effective.

On the basis of results from OCTAVIA,[17] which showed that the incidence of post-thrombotic syndrome was increased in patients with a low Villalta score who stopped elastic compression therapy early, we did a post-hoc analysis in a subgroup of patients from the IDEAL DVT trial with a Villalta score of 4 or less until 6 months. This analysis suggested that shorter duration of compression stocking use is also cost-effective in this subpopulation. Therefore, in these patients prolonged treatment might also be forgone.

The data for our economic study had some limitations. First, the number of patients who used some of the categories of care was small. Despite the large number of patients in the IDEAL DVT study population, the trial might therefore have been underpowered for some specific data categories. Nevertheless, the 95% CI of the incremental costs ranged from €5793 saved to €1241 saved, and the probability that individualised therapy duration was cost-effective was calculated to be 99%. Second, the time window for the economic analysis was limited to the 2-year duration of the study, so long-term consequences for cost-effectiveness are unknown. However, most patients who develop post-thrombotic syndrome are diagnosed with this syndrome within the first 2 years after deep vein thrombosis.[29] Although the consequences of post-thrombotic syndrome will extend beyond the time limit of our trial, the small difference in incidence of post-thrombotic syndrome at 2 years and the similarities in quality of life between groups shown in this analysis suggest that the likelihood of long-term negative effects on health is small. Third, the IDEAL DVT study design only allowed for shortened duration of compression therapy on the basis of Villalta score results after 6 months of therapy. Whether the duration of compression therapy can be reduced even further, with potential further implications for cost-effectiveness, could be the objective of further studies. Finally, because of the amount of missing data, we had to impute data to prevent a loss of statistical power and to decrease the probability of obtaining biased estimates. We used predictive mean matching (the only method that yields plausible imputations and preserves the original data distributions)[27] and the conclusions that we drew from analysis of complete data and imputed data were the same, so we are confident that the outcomes we present are robust. Some of the main strengths of this economic analysis are the large sample size, the low risk of bias because of the randomised nature of the IDEAL DVT trial from which the data were extracted, and the use of three instruments to obtain utilities to calculate QALYs, with consistent results between these calculations.

In conclusion, we showed that individualised duration of elastic compression therapy for prevention of post-thrombotic syndrome is a cost-effective strategy compared with the standard 2-year duration of compression stocking use. By using an individualised approach, substantial cost savings can be made, both from a health-care perspective and a societal perspective, without significant loss in health-related quality of life.

Contributors

EEA contributed to data collection, data analysis, data interpretation, and writing of the report. AJtC-H contributed to study concept and design, funding, recruitment of centres, data collection, data analysis, data interpretation, and writing of the report. MHP contributed to study design, funding, and writing and reviewing of the report. HtC contributed to study concept and design, funding, data collection, data interpretation, and writing of the report. MAJ contributed to the study design, funding, data analysis, data interpretation, and writing of the report. All other authors contributed equally to data collection, writing, and reviewing of the report.

Declaration of interests

We declare no competing interests.

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