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Residual vein occlusion in relation to immediate compression and post thrombotic syndrome in deep vein thrombosis

Short version: Residual vein occlusion in post thrombotic syndrome

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Key points

- Immediate compression therapy after deep venous thrombosis is associated with a 20% absolute reduction of residual vein occlusion.
- The reduction of residual thrombosis is associated with an 8% absolute reduction of post thrombotic syndrome at 24 months.

Abstract

Thus far the association between residual vein occlusion and immediate compression therapy and post thrombotic syndrome is undetermined. Therefore, we investigated whether compression therapy immediately after diagnosis of deep vein thrombosis affects the occurrence of residual vein obstruction, (RVO) and whether the presence of RVO is associated with post thrombotic syndrome and recurrent venous thromboembolism.

In a pre-specified sub study within the IDEAL DVT trial, 592 adult patients from 10 academic and non-academic centers across the Netherlands, with objectively confirmed proximal deep vein thrombosis of the leg, received no compression or acute compression within 24 hours of diagnosis of deep vein thrombosis with either multi-layer bandaging or compression hosiery (pressure 35mmHg). Presence of RVO and recurrent venous thromboembolism was confirmed with compression ultrasonography, incidence of post thrombotic syndrome as a Villalta score of $\geq$5 at 6 and 24 months. The average time from diagnosis until assessment of RVO was 5.3 (SD 1.9) months. A significantly lower percentage of patients who did receive compression therapy immediately after deep vein thrombosis had RVO, (46.3% versus 66.7%; OR 0.46 95% CI 0.27 to 0.80; p=0.005). Post thrombotic syndrome was less prevalent in patients without RVO (46.0 % versus. 54.0%; OR 0.65 95%CI 0.46 to 0.92; p=0.013). Recurrent venous thrombosis showed no significant association with RVO. Immediate compression should therefore be offered to all patients with acute deep venous thrombosis of the leg irrespective of severity of complaints. This study was registered at ClinicalTrials.gov (NCT01429714) and the Dutch Trial registry in November 2010 (NTR2597).

Introduction

While most guidelines for the management of deep vein thrombosis (DVT) emphasize the pharmacological treatment with anticoagulants and mainly focus on prevention of recurrent events, little attention is directed towards the prevention of long-term outcomes such as post thrombotic syndrome. [1-3]

Post thrombotic syndrome is the most frequent complication of DVT, affecting 20-50% of patients 1-2 years after DVT. [4-7] It is a chronic condition that is characterized by mild to severe symptoms and signs of venous insufficiency ranging from pain, sensation of leg heaviness, discomfort, pretibial edema, skin induration, hyperpigmentation, to venous ulceration in the most severe cases. The Villalta scale is a tool to diagnose and define the severity of post thrombotic syndrome using the above-mentioned signs and symptoms. [8] Due to its frequency, possible severity and chronicity, post thrombotic syndrome is not only costly but is also associated with a decrease in quality of life. [9-11] Currently, there is no cure for the condition; therefore acute treatment of DVT should include prompt prevention of post thrombotic syndrome.

Post thrombotic syndrome is thought to be a result of venous hypertension, caused by a combination of vein-wall remodeling, residual vein obstruction (RVO) and valvular reflux. [12, 13]. [14-16] The role of RVO as an independent risk factor for the onset of post thrombotic syndrome remains controversial. Known risk factors for post thrombotic syndrome are amongst others older age (RR 1.3-3; [5, 17-19], obesity (RR >2), [5, 17, 19, 20] history of ipsilateral DVT (RR 6-7),[18-22] proximal DVT (RR 2-3), [22, 23] pre-existing primary venous insufficiency (RR 1.2–1.8) [22] and inadequate international normalized ratio (INR) control during first 3 months of warfarin treatment (RR 2.7)[21].

The role of compression for the prevention of post thrombotic syndrome is undecided. A recent guidance for prevention of post thrombotic syndrome solely recommends optimal anticoagulant treatment of DVT with the use of pharmacologic agents or mechanical

thromboprophylaxis in high-risk patients.[24, 25] Once venous thrombosis has occurred, there is weak recommendation (class IIB) against routine use of elastic compression stockings to prevent post thrombotic syndrome. Nevertheless, a recent Cochrane meta-analysis showed that a 30% reduction in occurrence of post thrombotic syndrome could be achieved by application of compression stockings. [24-26] Elastic compression stockings are usually prescribed and fitted once the acute edema has resolved. Until then, it is customary in the Netherlands to offer early compression therapy in the form of multilayer compression bandaging or compression hosiery starting within 24 hours after DVT. The immediate compression phase typically comprises 4 weeks after the acute event of thrombosis and ends as soon as the edema is resorbed and compression stockings are fitted. To date, little is known about the effect of immediate compression in this early stage of the thrombosis; only three small, randomized controlled trials (n=45, n=69, n=73) have been published.[27-29] All these studies found an effect of direct compression therapy on occurrence of post thrombotic syndrome and recanalization on the short term. Moreover two of them reported faster reduction of pain and swelling with compression. However long-term effects were negative,[28] not assessed[29] or uncertain[27]. Furthermore, the effect of compression on occurrence of RVO, and the role of RVO in relation to risk of recurrence is not unequivocally clear.[30]

The aim of the current study is to investigate the effect of immediate compression therapy on the presence of RVO, and to assess the association of RVO with the incidence of post thrombotic syndrome 6 and 24 months after venous thrombosis as well as the association between RVO and recurrent venous thromboembolism within 24 months.

Methods

For this study, no separate ethical was needed or acquired, but data from the IDEAL study were used. For the IDEAL study, ethical approval was obtained by the institutional review board of Maastricht University Medical Centre and acknowledged by the ethical review

boards of participating centers (NL 32073.068.10). The trial was funded by a grant by ZonMw the Netherlands (grant number 171102007). The trial was registered at ClinicalTrials.gov number, NCT01429714. All participants gave written informed consent before any study related activity was performed.

Study design and population

The present study is pre-specified a sub study of the IDEAL DVT trial.

Briefly, the IDEAL DVT study was a randomized controlled non-inferiority trial that included 865 adult patients with objectively confirmed proximal DVT, without any history of previous ipsilateral venous thrombosis and without signs of venous insufficiency in 12 centers in the Netherlands and two centers in Italy. The study compared fixed duration of elastic compression therapy to tailored duration based on clinical signs and symptoms (the Villalta score). The study has been described in detail previously.[31] The current sub study assessed the presence of RVO at one week before cessation of anticoagulant treatment. Ten of the 12 Dutch centers that participated in the IDEAL DVT trial also participated in present study; the two Italian centers did not participate.

In the acute phase compression was initiated and executed according to three pre-specified protocols, one per participating center. One center followed the protocol of no initial compression, seven centers applied short stretch multilayer compression bandaging (thigh high with 30-40mmHg pressures applied) and two centers used compression hosiery (Mediven ®Struva35mmHg) initially until edema was resorbed and compression stockings were fitted. After this initial phase, all patients wore fitted compression stockings for 6 months. All patients participating in the RVO sub study were anticoagulated for a period of at least three months. The mean time within therapeutic range for the first 3 months of treatment for the patients anticoagulated with vitamin K antagonists within the ten study sites that participated in the sub study was provided by the anticoagulation clinics and calculated according to the Rosendaal method.[32]

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The outcomes

When discontinuation of anticoagulation was considered, independent radiologists in the participating centers performed compression ultrasonography to determine the presence of RVO, guided by a pre-specified protocol based on literature.[33] The patients were in a supine position, and the examined vein was imaged in a transverse plane. RVO was defined as the persistence of thrombotic material resulting in a diameter of at least 2 mm during full compression in either the common femoral vein at the groin or the popliteal vein in the popliteal fossa. The radiologists were required to describe the findings systematically according to one standard, provided by the study. Technical devices were dependent on hospital's preferences and availability. Post thrombotic syndrome was assessed using the ISTH consensus scoring method: a total Villalta score of $\geq$5 at least 6 months after the diagnosis of DVT. An independent radiologist objectively confirmed the occurrence of recurrent venous thromboembolism.

Statistical analysis

Baseline differences between the groups with and without compression in the acute phase were assessed based on Chi^2 test for categorical variables, and one-way ANOVA for continuous variables. The presence of RVO was analyzed as a binominal outcome. For the associations between RVO, compression in the acute phase of DVT and recurrent venous thromboembolism, multivariate logistic regression analyses was performed. Analyses were adjusted for statistically significant baseline differences: extent and type of thrombosis (provoked, unprovoked). Analyses were also adjusted for treatment effect after 6 months (individualized or standard duration of elastic compression stockings, the IDEAL intervention effect). Sensitivity analysis was performed with complete cases and by performing the

analyses restricted to the group of patients with DVT in the common femoral vein. The level of statistical significance was set at a p value of $\leq$0.05. The software program SPSS version 23.0 was used for all analyses.

Results

In total 592 patients with a mean age of 57.0 years (SD 15.0) participated in this study. The majority (57.8%) was male. The average body mass index was 28.2 km/m^2 (SD 5.3). A history of contralateral DVT was seen in 10.1%. In 52.2% of patients the DVT was located in the popliteal vein, followed by the femoral vein in 27.5% and the common femoral vein in 20.1%. The left leg was involved in 52.7%, the right leg in 46.5% and 0.8% of patients had bilateral DVT. The majority of patients (80.6%) were prescribed vitamin K antagonists, 3.0% received direct oral anticoagulants, 11.1% used investigational anticoagulants (either warfarin or rivaroxaban) and 4.4% used low molecular weight heparin monotherapy. The mean duration of anticoagulant therapy was 258 (SD 178) days. The meantime within therapeutic range for short-term anticoagulation therapy (first 3 months of treatment) was 74.03 % (SD 3.7) for the sites with immediate compression (both multilayer bandaging and compression hosiery) and 76.07(SD 4.6) for the site without initial compression. The average time from diagnosis to the assessment of RVO was 5.3 (SD 1.9) months. Table 1 provides the baseline characteristics of the study population for clinical characteristics.

Overall, in the acute phase 72 patients (12.2%) received no compression, multilayer compression bandaging was applied in 369 patients (62.3%) and compression hosiery was applied in 151 patients (25.5%). Statistically significant differences in the compression groups were observed in regard to thrombus location and type of DVT. In the non-compression group thrombus location was at the level of the popliteal vein in 39.4%, in 28.2% femoral and 32.4% common femoral. For the compression group, this was 54.0% (range across centers 43.9% to 65.0%), 27.5% (range across centers 0% to 43.9%) and 18.5% (range across centers 5.9% to 45.5%) respectively, p=0.014. Provoked DVT was

observed in 42.3% of the patients without compression and 29.3% (range across groups 13.3% to 48.5%) of the patients with compression therapy (p=0.046).

Compression in the acute phase and residual vein obstruction

In total 289 out of 592 patients (48.8%) had RVO on ultrasound (Table 2). Of the patients in the non-compression group, 66.7% had RVO compared to 46.3% of the patient that received compression therapy (47.4% for compression bandaging, 43.7% hosiery). This corresponds to an absolute reduction of 20.4% (OR 0.46 (95% CI 0.27 to 0.80) p=0.005 of RVO when compression therapy is applied in the acute phase.

Residual vein obstruction and post thrombotic syndrome

Table 3 illustrates the occurrence of RVO in relation to post thrombotic syndrome at 6 and 24 months after DVT, and recurrent venous thromboembolism at 24 months after DVT. At 6 months 55.7% of patients with post thrombotic syndrome had RVO compared to 44.3% without post thrombotic syndrome (OR 0.66 95% CI 0.46-0.96, p=0.029). The same trend was observed at 24 months: patients without post thrombotic syndrome had less often RVO (46.0%) than patients with post thrombotic syndrome (54.0%);OR 0.65; 95%CI 0.46-0.92, p=0.013). Sub group analyses with only patients who were diagnosed with DVT in the common femoral vein showed no significant effect of immediate compression in the acute phase on presence of RVO. RVO was observed in 65.2% of the patients with common femoral vein thrombosis in the no compression group, and in 64.6% of the patients with compression (OR 0,93 95%CI 0.35-2.43 p=0.579). RVO was also not significantly associated with post thrombotic syndrome at 24 months (OR 0.77 95% CI 0.54 to 1.12, p=0.186) in this subgroup of patients.

Residual vein obstruction and recurrent thromboembolism

No significant association between RVO and recurrent venous thromboembolism was observed (Table 3). A total of 30 recurrent events of DVT was observed during the study of

which 60 percent had RVO compared to 40% without RVO; OR 0.82 (0.61 to 1.12), p=0.263. Recurrent pulmonary embolism occurred in 19 patients in total of whom 52.6% had RVO, and 47.7% not; OR 0.95 (0.61 to 1.46) p=0.805).

Discussion

This study shows that starting compression treatment in the acute phase, as soon as 24 hours after the diagnosis of DVT, significantly reduces the absolute incidence of RVO with 20.4%. Moreover, the incidence of post thrombotic syndrome both at 6 and at 24 months was significantly lower in patients without RVO compared to patients with RVO with an absolute difference of 11.4% at 6 months and 8% at 24 months. This suggests that RVO does contribute to the development of post thrombotic syndrome and that compression therapy may prevent post thrombotic syndrome from the very early start of thrombosis treatment. The efficacy of both multilayer bandaging compression and compression hosiery was similar. Our data do not show a significant association of RVO with the occurrence of recurrent venous thromboembolism; the number of recurrences was however too low to allow for a definitive conclusion.

Our study has some weaknesses, first this is a sub analysis of data from a large randomized trial, and the study sample as such is not randomized. However, adjustments for differences in distribution of patient characteristics between the groups compared were made in the analyses. Furthermore, a small proportion of patients were anticoagulated with a direct oral anticoagulant or low molecular weight monotherapy. It has been suggested that these types of anticoagulation may influence the risk of post thrombotic syndrome. Another potential weakness is the fact that only assumptions can be made on the mode of action of compression; therefore the data do not allow inference for causality. There are however several strengths. First, this is the first study with a long term follow up of patients and with a sufficiently large sample size to provide reliable information on the clinical importance of early compression therapy following acute DVT. Second, the assessor-blinded design that

included frequent assessments of the leg provided sufficient and dependable data for analysis.

Only three studies have been performed on the efficacy of early compression therapy in the acute phase so far. One trial (n=45) randomized between inelastic bandages plus walking exercises, elastic compression stockings plus walking exercises, and no compression with bed rest.[27] After 2 years, less post thrombotic syndrome was seen in patients randomized to compression therapy and ambulation [34], it is uncertain whether this was the effect of early compression or walking exercises. Roumen et al randomized between immediate multilayer compression bandages and no compression before application of elastic compression stockings.[28] This study (n=69) found a reduction of symptoms and edema in the first week, but no difference in PTS after 1 year. The third trial (n=73) compared acute initiation of compression hosiery with hosiery starting after 14 days. [29] Better recanalization of the thrombus was detected at 14 and 90 days in patients in which acute initiation of hosiery was applied, but long-term effects on post thrombotic syndrome were not assessed. Hence, our study fills both the need for a larger sample size and the evaluation of long-term effects.

In the past decade, improvements have been achieved mainly in the pharmacological treatment of DVT in terms of reducing the risk of recurrence against a lower risk of bleeding. However, to date, no effective therapy in the acute phase is available to help restore venous patency and reduce the risk of long-term sequelae such as post thrombotic syndrome.

Our conclusion suggests that early compression treatment results in a lower incidence of residual vein thrombosis and consequently in less post thrombotic syndrome, and is in line with expectations based on the open vein hypothesis: “early thrombus resolution results in less post thrombotic syndrome because there is less vein wall damage due to the shorter duration that the thrombus is adjacent to the vessel wall”.

The use of early catheter directed thrombolysis to restore venous patency was expected to effectively reduce the risk of post thrombotic syndrome in selected patients with more

proximal extended thrombosis. However, so far thrombolysis has been consistently associated with an increased risk of bleeding, but its effectiveness has not been unequivocally proven. [34,35]

Compression therapy has virtually no contraindications and harbors no risk of bleeding. In our population, 119 patients (20.1%) were diagnosed with a proximal DVT in the common femoral vein. We found that especially in this subset of patients, early compression therapy might not be effective, highlighting the importance of correct identification of patients eligible for treatment strategies in the acute phase and the need for additional treatment options.

How precisely immediate compression therapy affects the recovery of venous patency cannot be answered by the current study. We may only hypothesize that mechanical compression reduces the vein diameter and thereby increases the venous return and as a result promotes thrombus resolution.[36, 37] Better venous return reduces edema and improves calf muscle function. [38] Moreover, compression therapy restores the microcirculation thereby promoting the inflammatory response necessary for thrombus resolution. Current guidelines suggest application of compression only in case patients experience complaints. [1] In alignment with this some clinicians only tend to apply immediate compression therapy if the patient presents with more severe symptoms of the DVT. The results of our study indicate however that immediate compression therapy should not only be applied in patients with increased symptomatology merely to reduce symptoms, but more importantly suggests that immediate compression should be applied in all patients even in those that are asymptomatic in order to prevent post thrombotic syndrome. That impaired thrombus resolution is an important driver in the onset of post thrombotic syndrome is also known from earlier studies showing that sub therapeutic anticoagulant therapy, and thereby insufficient inhibition of the formation of thrombin and activation of TAFI, is a risk factor for post thrombotic syndrome. [21] [39] Sub therapeutic INR was found to increase the risk of post thrombotic syndrome almost two-fold, while adequate anticoagulation therapy reduced the risk of post thrombotic syndrome by 11.9% (40) A risk reduction of the same order was found among patients using

direct oral anticoagulants compared to warfarin, but this was not statistically significant and needs further corroboration.[41] Also long-term treatment with low-molecular weight heparin in comparison to warfarin treatment has been shown to result in lower incidences of PTS. [42] The effect of immediate compression therapy is similar to the effect of improvement of anticoagulant therapy. In our sample the time within therapeutic range was found to be adequate and highly comparable between centers with and without immediate compression therapy.

We would like to suggest therefore that compression therapy should be added to new pharmacological strategies in order to achieve optimal prevention of post thrombotic syndrome. The application of immediate compression therapy within 24 hours of the diagnosis of DVT is common clinical practice in most Dutch hospitals. It is therefore shown that it is feasible to provide such care.

The cost-effectiveness for the application of immediate compression for all patients with acute DVT should be investigated. It may be anticipated that the application of multi-layer bandaging will be less cost-effective compared to compression hosiery. Furthermore, patients with iliofemoral DVT did not profit from immediate compression to the same extend as patients with less extensive DVT. Future research should be directed at better understanding of the underlying pathophysiology, and should be tailored to the individual patient's needs. The use of prediction models might assist doctors in the allocation of adjunctive treatment modalities to those who are likely to profit most.

In conclusion, we suggest that in addition to adequate anticoagulation therapy, immediate compression therapy - either with multilayer bandaging or with compression hosiery - should be implemented in daily clinical practice and that the application of early compression therapy in patients with acute DVT should be irrespective of symptomatology in order to optimize the prevention of post thrombotic syndrome. Furthermore, identification of patients

at increased risk of post thrombotic syndrome should be performed in the acute phase in order to be able to provide these patients with adjunctive treatment.

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Authorship

Contribution: The participating IDEAL investigators designed the study. EEA and AJtCH analyzed the data. EEA, IMB, MtW and AJtCH wrote the manuscript. The participating IDEAL investigators included patients and collected the data. All authors were involved in the study. All authors critically reviewed and approved the final manuscript.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work other than described above; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Tables

Table 1: Baseline demographic and clinical characteristics N=592	
Mean age, years (SD)	57.0 (15.0)
Male, N (%)	342 (57.8)
Mean body mass index, kg/m^2 (SD)	28.2 (5.3)
Previous DVT contralateral N (%)	70 (10.1)
Provoked thrombosis N (%)	182 (30.7)
DVT location N (%)	
Popliteal vein	309 (52.2)
Femoral vein	163 (27.5)
Common femoral vein	119 (20.1)
Left leg	312 (52.7)
Right leg	275 (46.5)
Bilateral	5 (0.8)
DVT treatment (%)	
Vitamin K antagonist (VKA) [†]	477 (80.6)
Non vitamin K anticoagulants (DOAC) [‡]	18 (3.0)
Investigational anticoagulants[§]	61 (11.1)
Low molecular weight heparin	26 (4.4)
Duration anticoagulant therapy (days)	258 (178)
Average time from diagnosis to second ultrasound, months (SD)	5.3 (1.9)
Compression therapy in the acute phase of DVT (%)	
No initial compression	72 (12.2)
Initial compression therapy	520 (87.8)
Multilayer compression bandaging	369 (62.3)
Compression hosiery	151 (25.5)

p vein thrombosis (DVT). [†]All patients with VKA had initially 5-10 days Low molecular weight heparin (LMWH). [‡]The only Direct Oral Anti Coagulants (DOAC) used during the study was rivaroxaban. [§]Some patients participated in studies comparing investigational anticoagulants (warfarin versus edoxaban), LMWH in patients with malignancy.

Table 2: Residual vein occlusion in relation to compression in the acute phase after DVT

	Compression									No compression		
	Compression*			Multilayer compression			Compression hosiery					
	N	**%**	**OR (95% CI)**	**N**	**%**	**OR (95% CI)**	**N**	**%**	**OR (95% CI)**	N	%	OR (95% CI)
Residual vein obstruction	241/520	46.3	0.46 (0.27-0.80)	175/369	47.4	0.48 (0.27-0.84)	66/151	43.7	0.42 (0.23-0.78)	48/72	66.7	-
No residual vein obstruction	279/520	53.7	-	194/369	52.6	-	85/151	56.3	-	24/72	33.3	-

Abbreviations: DVT, Deep vein thrombosis, analysis adjusted for thrombus location, type of deep vein thrombosis, and history of deep vein thrombosis. No compression was used as the reference group for all analyses.

Table 3: Residual vein occlusion in relation to PTS and recurrent venous thromboembolism

	No residual vein obstruction		Residual vein obstruction		OR (95%CI)
	N	%	N	%	
Post thrombotic syndrome at 6 and 24 months after DVT*					
Villalta score ≥5 at 6 months	77/174	44.3	97/174	55.7	0.66 (0.46-0.96)
Villalta score ≥5 between at 24 months	142/309	46.0	167/309	54.0	0.65 (0.46-0.92)
Recurrent venous thromboembolism between 6 to 24 months*					
Deep vein thrombosis	12/30	40.0	18/30	60.0	0.82 (0.61-2.12)
Pulmonary embolism	9/19	47.7	10/19	52.6	0.95 (0.61-1.46)

Abbreviations: PTS, post thrombotic syndrome; OR; Odds ratio; CI; confidence interval; DVT, deep vein thrombosis.

*Analyses adjusted for the intervention effect in IDEAL DVT study

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Residual vein occlusion in relation to immediate compression and postthrombotic syndrome in deep vein thrombosis

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