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ORIGINAL ARTICLE
VENOUS DISEASE

# Diosmin 600 in adjunction to rivaroxaban reduces the risk of post-thrombotic syndrome after femoropopliteal deep vein thrombosis: results of the RIDILOTT DVT study

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## ABSTRACT

**Background:** To assess the efficacy and safety of long-term diosmin 600 therapy added to rivaroxaban and elastic compression stockings (ECS) in patients with femoropopliteal deep vein thrombosis (DVT).

**Methods:** This single-center, open-label randomized clinical trial RIDILOTT DVT enrolled patients with their first femoropopliteal DVT confirmed by duplex ultrasound scan (DUS). Participants were randomly allocated to the control group (standard treatment with rivaroxaban for six months and ECS for 12 months) or the experimental group (standard treatment with the additional use of diosmin 600 mg once daily for 12 months). Patients were followed for 12 months. The primary outcome was post-thrombotic syndrome (PTS), according to the Villalta Score (≥5). The secondary outcomes were deep vein recanalization, chronic venous disease (CVD) progression, the severity of PTS (Villalta), and CVD (VCSS), quality of life (CIVIQ-20), venous thromboembolism recurrence, and adverse event (AE).

**Results:** Ninety patients were randomized (45 per group). There were 56 men and 34 women with a mean age of 57.8±13.4 years, and 69% had clinically unprovoked DVT. PTS frequency at 12 months was significantly lower (8.9% *vs*. 48.9%) in the experimental group compared with control one (relative risk, 0.14; 95% confidential interval, 0.04-0.43, P<0.001). Adding diosmin 600 was associated with quicker and complete vein recanalization, lower CVD progression rate, and lower Villalta, VCSS, and CIVIQ-20 scores. There was no difference in recurrent DVT or AE.

**Conclusions:** Adjunctive use of diosmin 600 to rivaroxaban and ECS in patients with femoropopliteal DVT can improve the clinical and ultrasound outcomes after 12 months of treatment.

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**Key words:** Diosmin; Inflammation; Post-thrombotic syndrome; Thrombosis.

For many decades, deep vein thrombosis (DVT) has been a significant medical and social problem with a substantial economic burden on developed countries' health care systems.[1, 2] According to official statistics, the incidence of DVT in the Russian Federation remained stable in 2014-2016, accounting for 1.5-1.6 cases per 1000 population per year,[3, 4] which is slightly higher than well-known epidemiological data.[5-9] The long-term outcome of DVT is a progression of chronic venous disease (CVD), *e.g.* progression of CEAP clinical class, exacerbation of the old or appearance of new symptoms and signs, that could develop into post-thrombotic syndrome (PTS), which significantly affects the patients' quality of life. The incidence of PTS in the 10-15 years after DVT reaches 19-42%, with skin ulceration in 3-4% of patients.[10-13] PTS usually develops within the first six months following the event.[10] Population studies in Russia showed that the prevalence of PTS was 1.4% of residents.[14]

The well-established PTS pathogenesis involves the destruction of the vein valves with the appearance of deep venous reflux, incomplete recanalization of the affected venous segments with the persistence of residual venous obstruction (RVO), impaired venous tonus because of vein wall inflammation and remodeling, or a combination of all mechanisms.[15] RVO was suggested to be the most important pathogenetic mechanism, which increases the risk of PTS development by 1.6-2.0 fold.[16-20] Recanalization of the affected vein is a complex biological process that involves natural immunity and inflammation that is responsible for clearance of the vessel lumen from the thrombus as well as venous wall lesions.[21, 22] Previous studies have shown that increased inflammatory biomarker levels, especially C-reactive protein, interleukins (IL)-6 and -8, intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1) are associated with a higher risk of PTS development.[23] These data raise the question of the possible pharmacological modulation of the inflammatory response that may protect the venous wall from excessive lesions while retaining the natural role of immune cells in the vessel recanalization.

Among the potential pharmacological agents with the ability to modulate the inflammatory reactions directly in the venous wall, flavonoids are of particular interest.[24-26] One of them is diosmin, a semisynthetic polyphenol (gamma-benzopyrone) produced from the citrus species. It has multiple modes of action, including venous tone, inflammatory process, capillary permeability, lymphatic drainage, free radical scavenges, blood viscosity, and rheology.[27] Previous experimental studies have demonstrated the ability of diosmin to block inflammatory reaction,[28] and a recent one suggested it could influence deep vein recanalization when associated with rivaroxaban.[29]

This study aimed to assess the efficacy and safety of long-term diosmin 600 mg therapy in addition to rivaroxaban and elastic compression stockings in patients with femoropopliteal DVT.

## Materials and methods

This single-center, open-label, randomized clinical trial with the masked assessor of efficacy outcomes, called Rivaroxaban with diosmin in the long-term treatment of DVT (RIDILOTT DVT; trial registration number NCT03413618) was performed at the Clinical Hospital No. 1 of the President's Administration of Russian Federation from December 2017 to July 2019. The study protocol was approved by the Institutional Review Board of Pirogov Russian National Research Medical University (certificate No.170, December 18, 2017).

The inclusion criteria were as follows: patients who presented with symptomatic provoked or unprovoked lower extremity DVT confirmed by duplex ultrasound scan (DUS); DVT localized in the femoropopliteal segment with possible involvement of common femoral vein and calf veins; patients over 18 years old; and signed informed consent.

Exclusion criteria were as follows: suspected or confirmed pulmonary embolism (PE); bilateral DVT; thrombus extension into the iliac veins above the inguinal fold as detected by DUS; contraindications for anticoagulants or diosmin (according to the official instructions); verified cancer at the time of DVT manifestation; known severe thrombophilia (protein C, protein S deficiency, antithrombin III, antiphospholipid syndrome); use of parenteral anticoagulants for 7 days or more; lack of elastic compression stockings (ECS) for 3 days or more; any interventional treatment of DVT (inferior vena cava filter, thrombectomy, catheter-directed thrombolysis); use of other drugs affecting hemostasis (except acetylsalicylic acid at a dose ≤100 mg per day), and expected poor compliance with the study protocol.

Based on the institutional protocol, all patients with suspected DVT were admitted to the emergency department and assessed using a two-level Wells Score and a D-dimer test to evaluate the clinical probability of thrombosis (Figure 1).[30] In patients with a Wells Score of ≥2 or a combination of Wells Score of ≤1 with positive D-dimer, anticoagulant therapy was initiated using low-molecular-weight heparin (LMWH) followed by DUS. Patients with

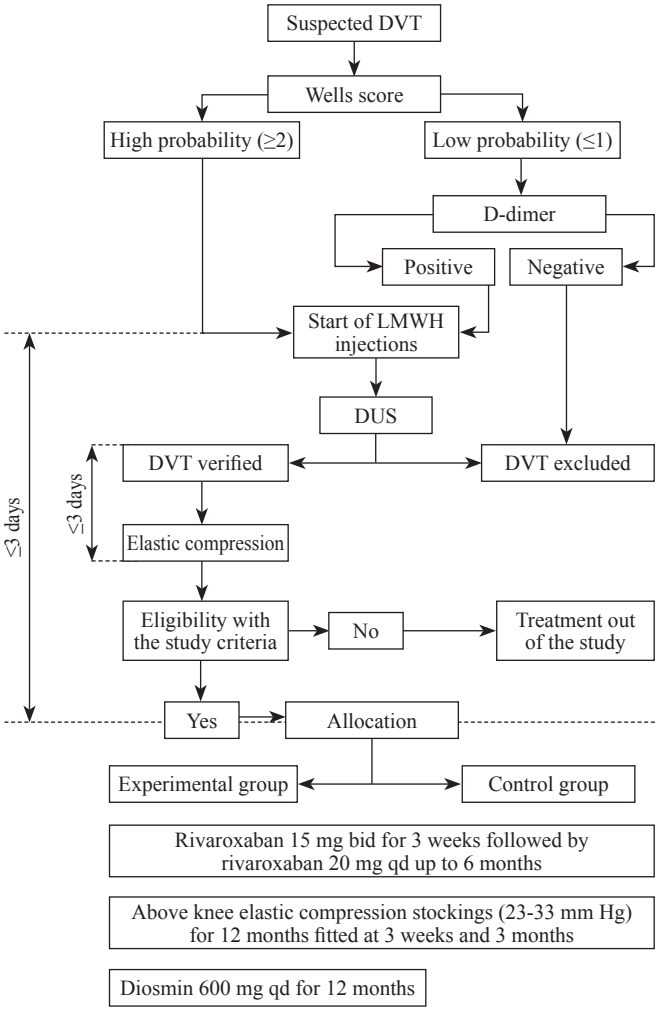


Figure 1.—The institutional diagnostic protocol for suspected DVT integrated into study design.
DVT: deep vein thrombosis; DUS: duplex ultrasound; LMWH: low-molecular weight heparins.

verified femoropopliteal venous thrombosis were assessed for eligibility according to the inclusion and exclusion criteria. After providing written informed consent, patients were randomly allocated to one of two groups (1:1) based on the number on the patient's medical record form: those with an even last digit were assigned to the experimental group, and those with an odd last digit were assigned to the control group; if the last digit was zero, the penultimate digit was used. The clinical center contains multiple medical departments of different specialties, and the numbering of the medical records is performed sequentially through all of them. Taking into account the large admission rate to all medical departments, there was an extremely low probability that two consistently included patients would have sequential medical records.

After randomization, a unique alphanumeric code was assigned to the patient, which allowed the blinded expert to evaluate the treatment results in an objective manner.

During the time from hospital admission to treatment allocation, all patients received therapeutic doses of LMWH (enoxaparin, 1 mg/kg twice daily). After randomization, patients in both groups were switched to the rivaroxaban at a dose of 15 mg twice daily for up to 3 weeks after administration of the first enoxaparin dose. The patients then received a dose of 20 mg once daily for up to six months. The first rivaroxaban dose was administered instead of LMWH at the time of the next scheduled injection. Additionally, within the first three days after the DVT diagnosis, patients in both groups started using above-knee elastic compression stockings with a pressure of 23-32 mmHg at the ankle (class 2 compression according to RAL-GZ 387). Above-knee ECS was used according to the local standards for the treatment of femoropopliteal DVT. The size of the stocking was matched to the diameter of the limb at three weeks and three months after starting treatment. Patients were advised to wear the stockings 24 hours a day for the first week and then during the day for the next 12 months. In the experimental group, patients received diosmin 600 mg (Phlebodia 600, Innotech, Arcueil, France; 1 tablet once daily) for the entire treatment period (12 months), in addition to the standard treatment. The first dose of diosmin was administered immediately after treatment allocation and in parallel to the switch to the rivaroxaban.

Patients were followed for 12 months after randomization with clinical and ultrasound evaluation every two months. At baseline, in addition to standard clinical data, the affected limb was evaluated for the presence of pre-existing chronic venous disease (CVD). If confirmed, the clinical class by CEAP classification (the version of 2004) was determined.[31] Clinical classes of C1-C2 and C4-C6 were confirmed objectively based on the presence of corresponding clinical signs. Clinical class of C3 was confirmed based on the patient's medical history (documented diagnosis, complaints of edema of the lower limb, *e.g.*, difficulties in wearing shoes due to changes of leg size in the evening, presence of strangulation lines, pittings, or need for compression therapy before the manifestation of thrombosis) because, at the time of physical examination, all patients had swelling resulting from acute DVT.

The patients were clinically evaluated with the attention paid to the adverse events (AE) of therapy every two months. At 6 and 12 months, the CEAP clinical class, the

VCSS Score,[32] the CIVIQ-20 Score,[33] and the Villalta Score[34] were evaluated.

DUS was performed using MyLab30 (Esaote, Genoa, Italy) with a linear ultrasound transducer LA532 in the frequency range of 5-13 MHz. The common femoral vein (CFV) and femoral vein (FV) were assessed in the supine position, the popliteal vein (PV) was assessed in the prone position, and the calf veins were assessed in a sitting position. At each examination, all accessible venous segments were subject to evaluation. The criteria for DVT were incompressibility of the vein during compression by the transducer and the absence of blood flow in the vein on the color flow doppler mode. To assess the thrombus burden, a modified Marder Score was used[35] (Table I). DUS was repeated every two months, and the recanalization degree on the CFV, FV, and PV was calculated based on their compressibility. This was achieved by measuring the vessel diameter without compression and at maximal compression at the narrowest point of each venous segment. The recanalization degree (RD) was calculated as follows:

$$[d(\text{no compression})-d(\text{maximal compression})]/d(\text{no compression}) \times 100\%$$

All measurements were repeated three times, and the average value was used for calculations.

The primary outcome was the presence of PTS at 12 months after randomization according to the Villalta Score, as follows: a score of 5 and more for any PTS; a score of 5-9 for mild PTS, a score of 10-14 for moderate PTS, or a score of 15 and more or presence of active venous ulcer for severe PTS.

The secondary outcomes included the presence of PTS at six months; symptomatic or asymptomatic DVT recurrence; symptomatic pulmonary embolism; change in CEAP clinical class (progression was defined as a transition from a lower clinical class to a higher class; regression was defined as a transition from higher class to lower class, and lack of change was defined as the persistence of the same clinical class); CVD severity as assessed by VCSS; complete vein recanalization (RD≥80%); change in RD for the CFV, FV, and PV; change in thrombus burden as assessed by the modified Marder Score; bleeding and/or other AE associated with therapy.

Table I.—*Ultrasound quantification of deep vein thrombosis by modified Marder Score.*

| Venous segment | Score |
|---|---|
| Iliac vein | 8 |
| Common femoral vein | 4 |
| Femoral vein | 4 |
| Deep femoral vein | 2 |
| Popliteal vein | 2 |
| Tibial trunk | 2 |
| Peroneal trunk | 2 |
| Tibial vein (both of the pair) | 1 (2) |
| Peroneal vein (both of the pair) | 1 (2) |
| Gastrocnemius vein (both medial and lateral) | 1 (2) |
| Soleal vein or other calf muscle vein | 1 |
| Great saphenous vein trunk | 2 |
| Small saphenous vein trunk | 1 |
| Maximal Score for one limb | 34 |

Symptomatic DVT recurrence was defined as an increase in edema, pain, or hyperemia in the affected lower limb or the occurrence of the same signs on the intact leg and was confirmed by DUS. The asymptomatic recurrence of DVT was defined as the re-occlusion of the previously recanalized venous segment, or primary occlusion of the previously intact venous segment revealed by DUS.

Complete recanalization was defined as the clearance of thrombotic masses by 80% or more (RVO <20% or RD ≥80%).

Bleeding related to anticoagulation was classified as major (according to the International Society on Thrombosis and Hemostasis criteria),[36] clinically relevant non-major (any episode not fulfilling the criteria of major bleeding, but resulting in anticoagulant withdrawal and/or requiring a specific medical intervention and/or leading to an unscheduled visit to physician), or minor (any episode not fulfilling the criteria of major or clinically relevant non-major bleeding). AEs relation with treatment was based on the investigator's judgment.

Specific measuring for compliance with rivaroxaban, diosmin, or ECS was not prespecified. Patients with expected low compliance with the study protocol (*e.g.* low social and education level, low mobility, logistic problems, army employment, dementia, alcohol abuse, etc.) were not enrolled according to the exclusion criteria.

The clinical and ultrasound outcomes on efficacy were assessed by the independent expert, who was masked to the patient's treatment allocation and had no access to the results of the previous investigation. He made a conclusion on the clinical (CEAP class, Villalta Score, VCSS Score) and ultrasound (vein occlusion, recanalization degree, Marder Score) status and sent it to the investigator. The safety outcomes were assessed by the investigator according to the treatment allocation.

The study was conducted with the financial support of the Laboratoire Innotech International (France). Laboratoire Innotech International did not influence study design, data collection, analysis, and interpretation, writing the report, the decision to submit the article for publication.

Deidentified individual participant data that underlie the reported results may be received by request. Proposals for access should be sent to the corresponding author.

## Statistical analysis

The prevalence of PTS at 12 months after index DVT treated with rivaroxaban was assumed as 30%.[10, 15] Taking into account the fact that adjunctive use of diosmin could provide a 70% reduction in the severity of CVD symptoms related to PTS at 12 months,[29] the absolute difference of 20% was assumed. Using Fisher's Exact test for primary statistical analysis, with a power of 80% and type I error of 0.05, the sample size was estimated as 120 subjects (60+60 in each group). We assumed that there would be an interim analysis when 50% of enrolled patients reached six months of follow-up with possible modification of the sample size. The interim analysis demonstrated an unexpected frequency of PTS in the control group and significant differences between groups, resulting in the premature completion of recruitment to reduce the harm for control subjects, with 90 participants enrolled. The principal statistical analysis was performed using IBM SPSS Statistics v.26 (IBM, Armonk, NY, USA) software package. The relative risk was calculated via MedCalc free web-interface (https://www.medcalc.org/calc/relative_risk.php). All absolute values are presented as the mean and standard deviation (mean±SD), categorical variables as an absolute number, percentage, and relative risk with 95% confidential interval (CI). Comparisons were performed by *t*-test, two-sided Fisher's Exact test, $\chi^2$ test, a general linear model for repeated measurements (GLM-RM), Adjusted and unadjusted Cox regression, and Kaplan-Meier statistics. P values below 0.05 were considered to be statistically significant.

## Results

During the inclusion period from December 2017 to June 2018, 202 patients with suspected DVT were admitted to the hospital, and the diagnosis was confirmed in 158 patients (Figure 2). Among them, 102 patients fulfilled the selection criteria, and 12 patients refused to participate. The remaining 90 patients were allocated to one of the two groups (N.=45 in each group). Their main demographical and clinical characteristics are presented in Table II. The

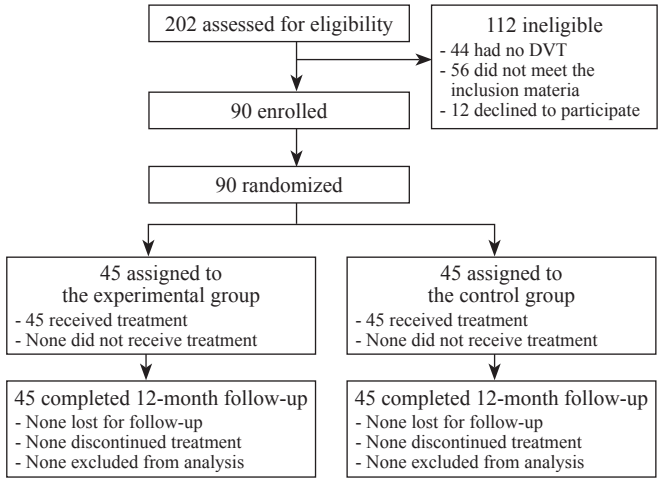


Figure 2.—Trial profile (CONSORT flow diagram).
DVT: deep vein thrombosis.

TABLE II.—*Characteristics of patients in the experimental and control groups.*

| Parameter | Experimental group (N.=45) | Control group (N.=45) |
|---|---|---|
| Age (mean±SD), years | 57.4±13.8 | 60.2±13.1 |
| Male, % | 62.2 | 62.2 |
| Clinically unprovoked DVT, % | 64.4 | 73.3 |
| Duration of symptoms by the time of hospital admission (mean±SD), days | 4.5±3.7 | 4.0±2.5 |
| Time from hospital admission to allocation (mean±SD), days | 3.4±1.2 | 3.5±1.6 |
| Pre-existing CVD, % | 51.1 | 71.1 |
| Class C0 | 17.8 | 17.8 |
| Class C1 | 31.1 | 11.1 |
| Class C2 | 37.8 | 53.3 |
| Class C3 | 13.3 | 8.9 |
| Class C4 | 0.0 | 8.9 |
| Lesions of the left limb, % | 48.9 | 60.0 |
| Thrombus extension | | |
| Common femoral vein lesion, % | 37.8 | 28.9 |
| Femoral vein lesion, % | 80.0 | 68.9 |
| Popliteal vein lesion, % | 100.0 | 100.0 |
| Thrombus burden by modified Marder Score (mean±SD), score | 15.2±4.7 | 11.6±4.1 |

DVT: deep vein thrombosis; SD: standard deviation; CVD: chronic venous disease.

control subjects had a higher rate of pre-existing CVD, in particular, CEAP clinical classes C2-C4. The involvement of CFV, FV, and PV was comparable in both groups, but the thrombus burden assessed by the modified Marder Score was higher in the experimental group because of more extensive lesions in the calf veins.

None of the study participants were lost throughout the follow-up period or prematurely completed the study. Thus, data from all 90 patients were analyzed. The interim analysis at six months (September 2018) showed PTS in 3 of 28 patients (10.7%) in the experimental group compared with 12 of 29 patients (41.4%) in control one (P=0.01). At 12 months, PTS was reported in 22 of 45 subjects (48.9%) who received standard anticoagulation and ECS compared with 4 of 45 patients (8.9%) who additionally received diosmin (relative risk, 0.14; 95% CI, 0.04-0.43; P<0.01). No severe forms of PTS were reported in either group. The mean Villalta and VCSS scores were lower in patients of the experimental group. The CIVIQ-20 Score also revealed an improved quality of life in the experimental group. Progression of pre-existing CVD was observed in one patient (2.2%) treated with diosmin and 11 patients (24.4%) without additional therapy (relative risk, 0.09; 95% CI, 0.01-0.68; P<0.01). The results are presented in Table III.

Recurrent DVT was reported in seven patients: one patient (2.2%) in the experimental group compared with six patients (13.3%) in the control group (relative risk, 0.17; 95% CI, 0.02-1.33). The time to event is represented in Figure 3 and Table IV. Six episodes occurred after cessation of anticoagulation. In four out of seven patients, recurrent DVT episodes did not have significant clinical symptoms, in three out of seven patients, it was a re-occlusion of previously recanalized veins. None of the patients with DVT recurrence were excluded from the data analysis.

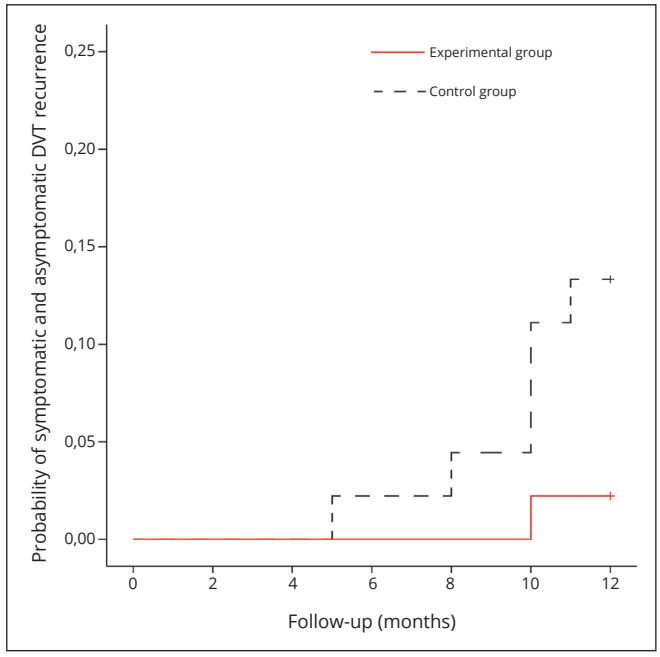


Figure 3.—Probability of symptomatic and asymptomatic deep vein thrombosis (DVT) recurrence.
Kaplan-Meier statistics and log-rank test (P=0.05).

TABLE III.—*Primary and secondary outcomes in the experimental and control groups.*

| Outcome | Experimental group (N.=45) | Control group (N.=45) | Relative risk (95% CI) | P value |
|---|---|---|---|---|
| Diagnosis of PTS at 12 months - N. (%) | 4 (8.9) | 22 (48.9) | 0.14 (0.04-0.43) | <0.01* ^ |
| Diagnosis of mild PTS at 12 months - N. (%) | 4 (8.9) | 18 (40.0) | 0.22 (0.08-0.61) | <0.01* ^ |
| Diagnosis of moderate PTS at 12 months - N. (%) | 0 (0.0) | 4 (8.9) | 0.11 (0.01-2.01) | 0.117 |
| Diagnosis of severe PTS at 12 months - N. (%) | 0 (0.0) | 0 (0.0) | NA | NA |
| Diagnosis of PTS at 6 months - N. (%) | 6 (13.3) | 23 (51.1) | 0.26 (0.12-0.58) | <0.01* ^ |
| Villalta at 12 months (mean±SD), score | 1.7±1.8 | 5.0±2.7 | NA | <0.01§ ^ |
| VCSS at 12 months (mean±SD), score | 1.2±1.1 | 4.4±2.1 | NA | <0.01§ ^ |
| CVD progression at 12 months - N. (%) | 1 (2.2) | 11 (24.4) | 0.09 (0.01-0.68) | <0.01* ^ |
| CIVIQ-20 at 12 months (mean±SD), score | 22.1±3.3 | 28.8±7.6 | NA | <0.01§ ^ |
| VTE recurrence at 12 months - N. (%) | 1 (2.2) | 6 (13.3) | 0.17 (0.02-1.33) | 0.11* |
| Symptomatic VTE recurrence at 12 months - N. (%) | 0 (0.0) | 3 (6.7) | 0.14 (0.01-2.69) | 0.24* |
| Bleeding at 12 months - N. (%) | 3 (6.7) | 4 (8.9) | 0.75 (0.18-3.16) | P>0.99* |
| Major - N. (%) | 0 (0.0) | 0 (0.0) | NA | NA |
| CRNM - N. (%) | 1 (2.2) | 2 (4.4) | 0.50 (0.05-5.32) | P>0.99* |
| Minor - N. (%) | 2 (4.4) | 2 (4.4) | 1.00 (0.15-6.79) | P>0.99* |
| Other adverse event - N. (%) | 2 (4.4) | 0 (0.0) | 5.1 (0.3-103.5) | 0.50* |

SD: standard deviation; PTS: post-thrombotic syndrome; CEAP: Clinical, Etiological, Anatomical, and Pathological classification; CIVIQ-20: Venous Disease Quality of Life Questionnaire; VCSS: Venous Clinical Severity Score; VTE: venous thromboembolic event; CRNM: clinically relevant non-major bleeding; NA: non available.
Statistics: *Fisher's Exact test; § *t*-test; ^statistically significant differences.

TABLE IV.—*Characteristic of recurrent DVT.*

| N. | Location | Signs and symptoms | Time (months) | Treatment strategy | Thrombus burden analysis |
|---|---|---|---|---|---|
| 1 | Contralateral limb | Symptomatic | 5 | Switched to LMWH/VKA | Only the primarily-affected limb evaluated |
| 2 | Contralateral limb | Asymptomatic | 8 | Resumption of therapy | Only the primarily-affected limb evaluated |
| 3 | Ipsilateral popliteal vein re-occlusion | Asymptomatic | 10 | Resumption of therapy | *Evaluated until eight months* |
| 4 | Ipsilateral popliteal vein re-occlusion | Asymptomatic | 10 | Resumption of therapy | *Evaluated until eight months* |
| 5 | Ipsilateral popliteal vein re-occlusion | Symptomatic | 10 | Resumption of therapy | *Evaluated until eight months* |
| 6 | Contralateral limb | Asymptomatic | 10 | Resumption of therapy | Only the primarily-affected limb evaluated |
| 7 | Ipsilateral great saphenous vein extended to common femoral vein | Symptomatic | 11 | Resumption of therapy | Evaluated without taking into account the new common femoral vein lesion |

TABLE V.—*Ultrasound outcomes in the experimental and control groups.*

| Outcome | Experimental group | Control group | P value |
|---|---|---|---|
| Thrombus burden by modified Marder (mean±SD), score | | | |
| Baseline | 15.2±4.7 | 11.6±4.1 | <0.01^ |
| 2 months | 8.5±4.9 | 7.1±3.2 | 0.11 |
| 4 months | 4.5±2.9 | 4.6±2.7 | 0.82 |
| 6 months | 0.5±1.4 | 2.4±3.1 | <0.01^ |
| 8 months | 0.4±1.1 | 1.9±2.4 | <0.01^ |
| 10 months | 0.3±1.0 | 1.9±2.4 | <0.01^ |
| 12 months | 0.3±1.0 | 1.9±2.4 | <0.01^ |
| Recanalization degree (mean±SD) | | | |
| Common femoral vein | N.=17 | N.=13 | |
| Baseline | 21.2±31.0 | 18.5±29.1 | 0.81 |
| 2 months | 85.9±28.0 | 66.2±35.2 | 0.10 |
| 4 months | 90.6±25.7 | 70.8±33.8 | 0.08 |
| 6 months | 95.0±20.0 | 84.6±31.5 | 0.32 |
| 8 months | 96.9±5.0 | 93.8±22.1 | 0.65 |
| 10 months | 98.8±5.0 | 93.8±22.1 | 0.40 |
| 12 months | 98.8±5.0 | 93.8±22.1 | 0.40 |
| Femoral vein | N.=36 | N.=31 | |
| Baseline | 0.0 | 1.6±8.9 | 0.33 |
| 2 months | 63.9±33.7 | 52.4±37.3 | 0.15 |
| 4 months | 88.2±24.0 | 57.4±32.5 | <0.01^ |
| 6 months | 96.4±17.3 | 85.5±26.1 | 0.05 |
| 8 months | 97.2±16.7 | 88.1±23.7 | 0.08 |
| 10 months | 98.1±11.7 | 88.1±23.7 | 0.04^ |
| 12 months | 98.1±11.7 | 88.1±23.7 | 0.04^ |
| Popliteal vein | N.=45 | N.=45 | |
| Baseline | 0.0 | 0.0 | - |
| 2 months | 52.0±28.8 | 39.3±24.7 | 0.03^ |
| 4 months | 74.9±29.4 | 56.5±26.9 | <0.01^ |
| 6 months | 90.0±25.0 | 73.6±28.2 | <0.01^ |
| 8 months | 93.1±21.1 | 73.6±28.2 | <0.01^ |
| 10 months | 93.3±19,9 | 78.4±23.3 | <0.01^ |
| 12 months | 95.1±17.3 | 78.7±22.9 | <0.01^ |

Experimental group, N.=45; control group N.=45.
(N.=45)SD: standard deviation;
Statistics: *t*-test; ^text in bold represents statistically significant differences.

There were no serious AEs, including major bleeding, in either group. Clinically relevant, non-major bleeding was present in one patient in the experimental group who had hemorrhoidal bleeding and one hemorrhoidal bleeding plus one hematuria in the control group. Additionally, four patients with minor bleeding were reported (two in each group): rectal bleeding plus epistaxis in the experimental group and epistaxis plus ecchymosis in the control group. In terms of other AEs, two patients in the experimental group experienced mild dyspepsia related to diosmin, which did not require any specific medical help or discontinuation of the experimental treatment (Table III).

Results of vein recanalization are presented in Table V and Figure 4. In both groups, there was a significant trend towards the restoring of vein patency over time (P<0.01). The significant difference in the speed of recanalization was revealed in the PV, and complete recanalization was achieved in 93.3% of patients in the experimental group compared with 62.2% of patients in the control group (P=0.01). The recanalization of the FV occurred significantly faster, and the vessel patency was restored more often in the experimental group (97.2% *vs*. 77.4%; P=0.02). No difference between groups was observed in the CFV (100% of patients in the experimental group *vs*. 92.3% of patients in the control group restored full vein patency; P=0.45).

A significant difference between the groups was observed for the changes in thrombus burden, as assessed by the modified Marder Score (Table V and Figure 5). At baseline, the extent of thrombus in the experimental group was significantly greater (15.2±4.7 *vs*. 11.6±4.1; P<0.01), but after 12 months of therapy it was significantly lower (0.3±1.0 *vs.* 1.9±2.4; P<0.01) compared with the control group. These findings suggest that long-term use of diosmin in addition to standard anticoagulation with rivaroxaban could provide a faster reduction in thrombus burden.

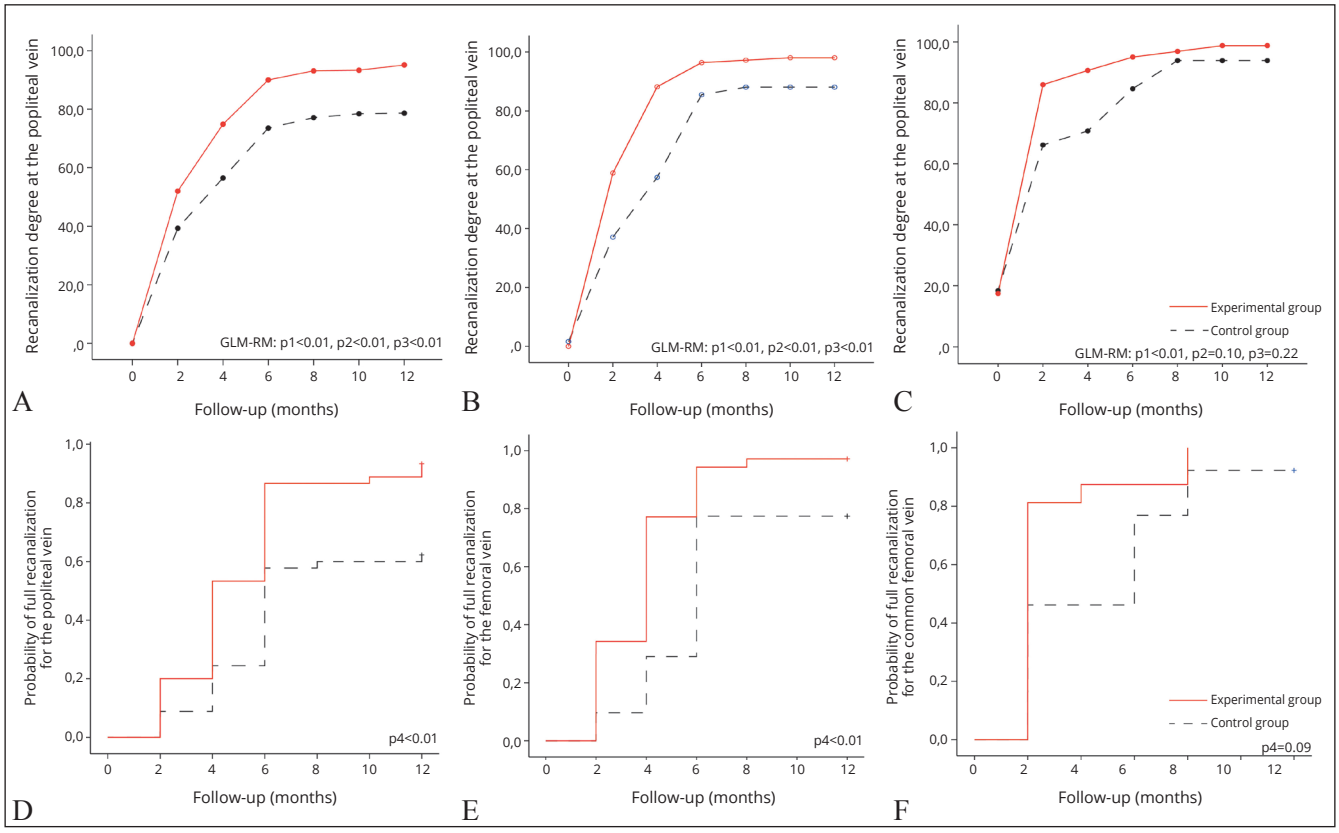


Figure 4.—The recanalization of the main venous segments. Changes in recanalization degree at the popliteal vein (A), femoral vein (B) and common femoral vein (C). Probability to achieve full recanalization (recanalization degree ≥80%) for the popliteal vein (D), femoral vein (E), common femoral vein (F).
GLM-RP (generalized linear model repeated measures): p1, within-subject effect "time"; p2, within-subject interaction "time×group"; p3, between-subject effect "group"; p4 - log-rank test for Kaplan-Meier statistics.

Secondary statistical analysis for the primary outcome (Table VI) and subgroup analysis (Figure 6) showed the consistency of the results. The risk of PTS was significantly decreased in both subgroups of patients independently to pre-existing CVD. The cumulative incidence of newly diagnosed PTS appeared to be higher than the final figures. The reason is that during the last six months of observation, symptoms and signs of CVD decreased in three patients received diosmin with ECS and in one subject received ECS alone, so they fell out of PTS Villalta criteria at 12 months.

## Discussion

Recanalization of the affected vein is a complicated biological process, involving an immune inflammatory reaction that recruits a large number of neutrophils, monocytes, and lymphocytes.[21, 22] Restoration of vein patency occurs by direct clot lysis with activated plasminogen, thrombus fragmentation by endothelial lytic activity, and thrombus contraction and retraction resulting from collagen formation on the framework of fibrin fibers and the appearance of myofibroblasts, and also through the creation of new channels that are lined with endothelium and that are located directly in the thrombotic mass.[37] Early thrombus resolution strongly correlates with the preservation of deep vein valvular function.[38]

Early DVT treatment with vitamin K antagonists (VKA) was associated with the absence of a reduction in thrombus burden at 3-6 months in 23% of patients.[39] The long-term use of LMWH compared with VKA increased the chance of complete vein recanalization 1.5-fold and reduced the risk of PTS by 23%.[40] This effect may be related to the pleiotropic properties of LMWH and the presence of anti-inflammatory action.[41] Direct oral anticoagulants, particularly rivaroxaban, are associated with a higher rate of deep vein recanalization and a lower risk of

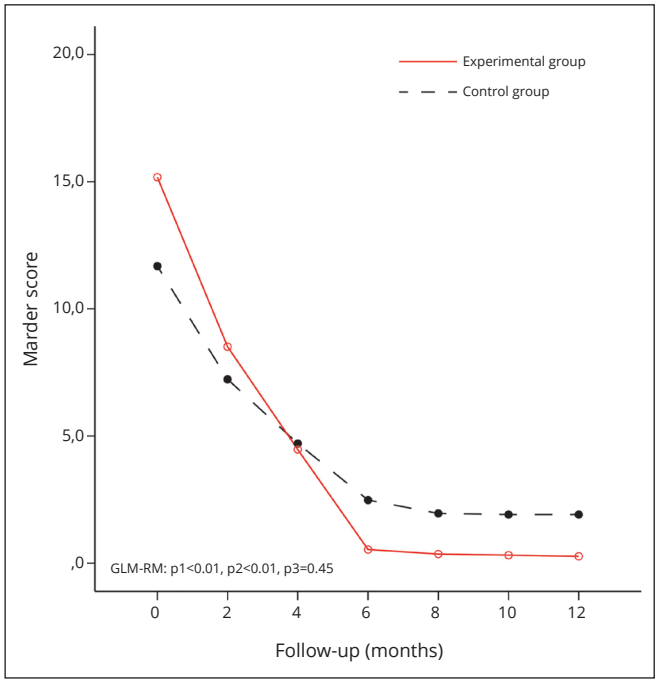


Figure 5.—Changes in the thrombus burden as assessed by the modified Marder Score.
GLM-RP (generalized linear model repeated measures): p1, within-subject effect "time"; p2, within-subject interaction "time×group"; p3, between-subject effect "group".

PTS compared with VKA.[42-45] The exact mechanisms of action are not completely understood, but it was assumed that rivaroxaban has specific anti-inflammatory activity through the protease-activated receptors.[46-48] It was previously reported that the anti-inflammatory profile of flavonoids, particularly diosmin, could influence the deep vein recanalization.[24-26, 29] These properties could allow the improvement of the long-term outcomes of DVT using the conservative treatment and may reduce the incidence of PTS at 12 months. Additionally, the number needed to treat (NNT) with diosmin 600 mg to prevent 1 case of PTS could be 2.5, while the number needed to harm (NNH) to cause 1 case of mild dyspepsia was 23 patients.

The observed incidence of PTS at the top of standard therapy (50%) was higher than the predicted one (30%) and resulted in the premature completion of recruitment.[10, 15] This may be related to the high incidence of recurrent DVT and the prevalence of pre-existing CVD. Ipsilateral DVT recurrence has been established as the main risk factor for PTS development,[15] and the rate of subclinical vein re-occlusion in the presence of RVO may be as high as 23% per year after cessation of anticoagulation.[49] In the current study, four out of seven recurrent

TABLE VI.—*Secondary statistical analysis of the primary outcome.*

| Variable | Experimental group (N.=45) | Control group (N.=45) |
|---|---|---|
| Postthrombotic syndrome[a] - N. (%) | 7 (15.6%) | 23 (51.1%) |
| Relative risk (95% CI) [a] | 0.30 (0.14-0.64) | reference |
| Unadjusted Cox hazard ratio (95% CI) [a,b] | 0.30 (0.13-0.70) | reference |
| Adjusted Cox hazard ratio (95% CI) [a,b,c] | 0.31 (0.13-0.73) | reference |
| Adjusted Cox hazard ratio (95% CI) [a,b,d] | 0.30 (0.10-0.90) | reference |

[a]All cases of newly diagnosed PTS at 6 or 12 months up taken into account (cumulative incidence); [b]patients are censored by the time of newly diagnosed PTS; [c]adjusted by pre-existing CVD; [d]adjusted by sex, age, leg side, clinical provocation, duration of LMWH administration, initial Marder Score, lesion of CFV and FV, pre-existing CVD.

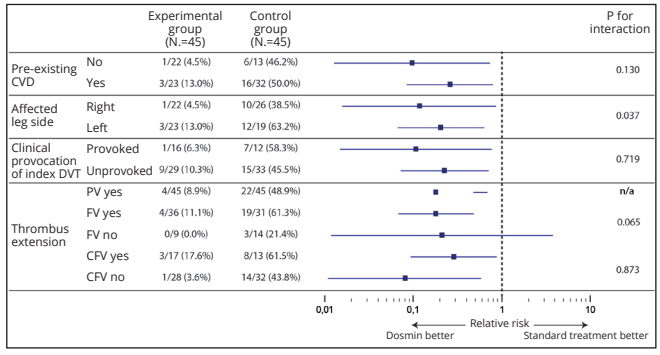


Figure 6.—Results of subgroup analysis.
P calculated with Cox hazard model for cumulative incidence of PTS censored on time of detection.
CFV: common femoral vein; CVD: chronic venous disease; DVT: deep vein thrombosis; FV: femoral vein; PV: popliteal vein.

DVT episodes were asymptomatic, and three of them presented with re-occlusion of the popliteal vein. PTS was observed in 21 of 83 patients (25.3%) without recurrent DVT compared with 5 of 7 patients (71.4%) with the recurrence (relative risk, 2.82; 95% CI, 1.55-5.13; P=0.02).

History of CVD is another important risk factor for PTS development. On the one hand, DVT can promote CVD progression, but on the other hand, the Villalta Score appears to be very sensitive to pre-existing CVD that reflects with misdiagnosis of PTS in 42% of all cases.[49] The patients in the control group at baseline showed a higher prevalence of pre-existing CVD. The single-factor regression analysis, as well as adjusted Cox regression, did not reveal any strong influence of CVD on the primary outcome. PTS was reported in all 12 patients (100%) with CVD progression, and in 14 of 78 patients (18%) with stable or regressive disease (relative risk, 7.1; 95% CI, 3.5-9.0; P<0.01). Perhaps, the progression of CVD according to the CEAP clinical class is more strong criteria for PTS detection than the Villalta Score, which includes both objective signs and

subjective symptoms. However, long-term treatment with diosmin allowed to detain the progression of CVD signs by 90%. Also, the well-established ability of diosmin to relieve venous symptoms could be reflected in lower Villalta scores due to its subjective part.[50]

Finally, the significant difference between groups was observed only for mild PTS but not for moderate or severe forms. Thus, the social-economic impact of suggested treatment should be confirmed in further trials. However, at 12 months after index DVT quality of life assessed with CIVIQ-20 scores in patients treated with diosmin was significantly higher.

### Limitations of the study

This study has some important limitations. The quasi-randomization was performed in an old-fashioned open manner, and the allocation of the patient could be predicted by the number of the medical record. To reduce this methodological bias, all excluded patients were repeatedly reviewed by an independent expert for their eligibility. In the absence of placebo control, the blinded assessor could receive information on the patient's affiliation to the experimental or control group. To overcome this bias assessor was obliged not to ask such questions and not to storage results of previous examinations. Moreover, the clinical outcomes are supported by ultrasound data obtained by a blinded expert without access to the previous DUS reports. The Villalta Score is well established but not an accurate instrument for PTS verification. However, it was supported by the CVD progression by CEAP clinical class. The measuring for compliance with suggested treatment was not prespecified, but expectedly low-compliant patients were excluded. Despite the achievement of a significant difference in the primary outcome, the power of the study was insufficient to completely differentiate between groups for some clinical factors, among which the thrombus extension and the presence of pre-existing CVD. Also, the study was not powered for the analysis of secondary outcomes. The interim analysis was based on the secondary outcomes that resulted in a decreased sample size. These limitations must be overcome in subsequent studies.

## Conclusions

The results of this study suggest that diosmin 600 in addition to rivaroxaban and elastic compression stockings to treat femoropopliteal DVT decreased the incidence of PTS, decreased the rate of CVD progression, and improved deep vein recanalization without serious AEs, but it must be confirmed by a pivotal study.

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