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ORIGINAL RESEARCH

The Effects of 3-Month Rosuvastatin Adjuvant Therapy on Post Thrombotic Syndrome following Deep Vein Thrombosis; a Randomized Clinical Trial

Mehdi Pishgahi[1], Shirin Ghane Fard[2], Rahil Lak Tabriz[1], Kimia Karimi Toudeshki[1]*, Zahra Talebi[3]

1. Department of Cardiology, Shohadaye Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
2. Pediatric Endocrinologist, Shohadaye Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
3. School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

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Abstract: **Introduction:** Statins are known to have anticoagulation and anti-inflammatory effects. This study aimed to investigate the effect of Rosuvastatin in reduction of post thrombotic syndrome (PTS) following deep vein thrombosis (DVT). **Methods:** In this randomized clinical trial, patients who were diagnosed with DVT of lower extremity were randomly assigned to 4 treatment groups: group 1: Warfarin, group 2: Warfarin + Rosuvastatin, group 3: Rivaroxaban, and group 4: Rivaroxaban + Rosuvastatin. The treatments were followed for 3 months and prevalence of PTS (as primary outcome), as well as the changes in serum levels of D-dimer and C reactive protein (CRP), and the extent of thrombosis before and after the intervention (as secondary outcomes) were compared between groups. **Results:** 182 patients with the mean age of 55.22 ± 4.1 years finished the trial period (51.64% male). There was no significant difference between the groups regarding the baseline characteristics. Based on the Brandjes score, 31 (17.03%) patients had PTS at the end of the study. The occurrence of PTS was significantly lower in the groups taking statins ($p<0.0001$). Although the change in the mean difference of legs circumference before and after intervention, were significant in all groups ($p < 0.05$), the differences was more prominent in groups 2 and 4 ($p < 0.0001$). After 3 months of taking medication, decrease of CRP was more prominent in the statin groups ($p = 0.001$), and most cases with normal CRP were in statin groups. Among the patients with the serum D-dimer level above 10000 ng/mL, patients in the statin groups experienced significantly more reduction in D-dimer levels than the other groups ($p<0.001$). **Conclusion:** Rosuvastatin administration in combination with rivaroxaban or warfarin significantly reduces the level of inflammatory factors including CRP and D-dimer, compared to patients receiving anticoagulants alone. Rosuvastatin administration can significantly reduce the incidence of PTS and cause a difference in the size of the lower limbs within 3 months.

Keywords: Venous thrombosis; Postthrombotic syndrome; Rosuvastatin calcium; Rivaroxaban; Warfarin; Anticoagulants

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1. Introduction

Deep vein thrombosis (DVT) and acute pulmonary embolism (PE) are two presentations of venous thromboembolism (VTE). DVT can impose a significant burden on the patient's life; especially when it leads to pulmonary embolism (1). It has been reported that DVTs of the proximal veins of the lower extremities may be more likely to create edema compared to others; resulting in different circumferences of the lower limbs in unilateral cases (2). DVT treatment mainly involves anticoagulation when there is no contraindication. Afterwards, measures are taken to prevent future recurrences, embolism, and thrombosis-related complications (1). It has been shown that treatment with novel oral anticoagulants (NOACs) reduces the duration of hospitalization of patients in comparison to low molecular weight heparin (LMWH), warfarin or unfractionated heparin (UFH) (3). Post Thrombosis Syndrome (PTS) is the most common long-term complication of deep venous thrombosis (DVT) (4). PTS is the result of chronic venous insufficiency, which develops following deep vein thrombosis (DVT). This chronic venous

* **Corresponding Author:** Kimia Karimi Toudeshki; Cardiology Department, Shohada-e-Tajrish Hospital, Qods Sq., Tajrish, Tehran, Iran. Tel: (+98)2122718000, Email: kymya77@yahoo.com, ORCID: https://orcid.org/0000-0001-7560-7091.

insufficiency is due to valvular incompetence and venous hypertension that follows the thrombotic obstruction. Elevated D-dimer level is commonly used as a predictor of post-thrombotic syndrome, since it is the consequence of persistent activation of clotting or inflammatory pathways (5). PTS significantly reduces the quality of life with a wide range of adverse effects from minor inflammation, edema, and pain to severe complications such as venous stasis ulcers (6).

Patients with extensive DVT, recurrence of thrombosis on the same side of the body, a history of varicose veins, obesity, or residual thrombosis are at increased risk of developing PTS (6).

The best treatment strategy for prevention of PTS is still unclear (7). Maintaining an appropriate International Normalized Ratio (INR) for Warfarin, use of the Catheter Lysis method, and long-term treatment with low molecular weight heparin (LMWH) are suggested to reduce the risk of developing PTS (8, 9).

On the other hand, The JUPITER trial (2009) demonstrated a significant improvement in non-hyperlipidemic DVT patients, with elevated C-reactive protein (CRP) levels, when treated with rosuvastatin. In addition to decreasing cholesterol levels and CRP, treatment with statin seems to influence the process of coagulation by inhibiting tissue factor activity and activating platelets by reducing the expression of CD40L or P-selectin (10). But the ability of statins to reduce the incidence of PTS is still unclear for physicians and researchers. San Norberto et al. evaluated the use of statin therapy (rosuvastatin 10 mg or 5 mg) in prevention of PTS in DVT patients over 70 years old (11). In this study, although a statistically significant difference in the primary outcome (D-Dimer) was not observed, a significant reduction in serum CRP levels and the incidence of PTS was seen in participants treated with rosuvastatin (Villalta score higher than 5, 38.3% vs. 48.5%, p =0.019) (11). It has been hypothesized that inflammatory mediators released due to thrombus formation may induce valvular damage, leading to PTS (12-14). Also, a positive association between level of inflammatory markers (such as CRP, and intercellular adhesion molecule 1 (ICAM-1)) with PTS development have been reported. Considering the effect of rosuvastatin for inhibition of ICAM-1 expression (15), the idea of investigating its effect on prevention of PTS may be considered.

Statins are easy to use, cheap and very safe and do not increase the risk of bleeding; and according to available data, they can be valuable in the treatment and prevention of recurrence of VTE. This study aimed to evaluate the effect of rosuvastatin adjuvant therapy along with common anticoagulants on the improvement of treatment outcome and reduction of PTS incidence in patients with acute DVT.

2. Methods

2.1. Study design and setting

This randomized controlled trial was conducted on patients with established acute DVT, admitted to Shohadaye Tajrish, Modarres, and Labbafi Nejad Hospitals (affiliated to Shahid Beheshti University of Medical Sciences), Tehran, Iran, from September 25, 2017 to September 20, 2018 to evaluate the effects of rosuvastatin on 3-mounth outcomes.

The study protocol was approved by Research Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.REC.1396.651), registered in Iranian Registry of Clinical Trials (IRCT20150621022852N4), and conducted adhering to principles of Helsinki Declaration. Patients were assured that all information will remain confidential and anonymous. All patients provided written informed consent for participation.

2.2. Participants

Inclusion criteria consisted of age over 18 and established acute DVT diagnosed via Doppler ultrasonography by an expert attending radiologist. Patients with End-Stage Renal Disease (ESRD) who underwent routine dialysis and/or patients with glomerular filtration rate (GFR) below 30mL/min/1.73 m2, patients diagnosed with cancer before or during the trial, conditions such as infections and/or sepsis, which could affect serum inflammation factors and D-dimer levels, those with prior statin use, a contraindication for statin therapy (such as liver disease, severe myopathy during the treatment, etc.), bilateral DVT, loss to follow-up during the 3 months of trial for any reason including unwillingness of participants, and death during the trial period, were excluded. In addition, patients with chronic or acute on chronic DVT (based on the ultrasonography results) were also excluded.

2.3. Data gathering and intervention

Demographic data and patient history were obtained through patient interviews and extent and area of thrombosis were determined via physical exam and Doppler ultrasonography. Diagnostic tests such as Serum CRP level, Serum D-dimer, assessment of thrombosis area with Doppler ultrasonography (by an attending radiologist unaware of patient allocations) were performed. Computer software was used for permuted block randomization of patients into 4 groups (with 52 patients in each group) for treatment regimen allocation:

Group 1: Warfarin; Group 2: Warfarin + Rosuvastatin; Group 3: Rivaroxaban; Group 4: Rivaroxaban + Rosuvastatin.

The first arm received warfarin following initial heparin infusion, the standard therapy, with the aim of reaching the target INR of 2-3. In the second arm, in addition to warfarin,

rosuvastatin 20mg (Rosurexin® tablet 20mg, manufactured by ACTOVERCO Pharmaceutical Factory, Karaj, Iran) was administered once daily. The third arm received rivaroxaban 15mg twice a day in the first 3 weeks and then 20mg once daily. In the fourth arm, rosuvastatin was added to rivaroxaban regimen for treatment with the dosage mentioned previously. Dose was adjusted for patients with renal impairment. Use of compression stockings was advised for all patients according to treatment protocols in time with the initiation of medications. All patients were followed up every 2 weeks by phone for adherence to treatment regimen. After 3 months, CRP and D-dimer levels, difference in swelling between two calves-diameter of circumference of calf 4 cm below the tuberosity of tibia bone, and occurrence of PTS were assessed again for all patients and the results were compared to previous data of the patient and the data from other groups. If the patients had infections in their second visit for CRP assessment, the assessment was postponed for another 2 weeks.

In this study, the occurrence of PTS was confirmed based on Brandjes criteria, which consists of two sets of subjective and objective items. Subjective items (symptoms) include spontaneous pain in calf, spontaneous pain in thigh, pain on standing/walking, pain in thigh on standing/walking, edema of foot/calf, heaviness of leg, spontaneous pain and pain on walking/standing, and impairment of daily activities; each one having one point. Objective items (signs) include calf circumference increase by 1 cm, ankle circumference increase by 1 cm, pigmentation, venectasia, newly formed varicosis, phlebitis, and venous ulcer; each one having one point except the venous ulcer, which has 4 points. Patients with a score of 3 are considered mild, while 4 is considered moderate, and scores 5 or more or any score along with ulceration of the limb are considered severe PTS.

2.4. Outcomes

The treatments were followed for 3 months and prevalence of PTS (as primary outcome), as well as the changes in serum levels of D-dimer and C reactive protein (CRP), and the extent of thrombosis before and after the intervention (as secondary outcomes) were compared between groups.

2.5. Statistical analysis

According to literature, and considering an improvement rate of 0.33-0.65, and using the G power software, the minimum of 38 patients were allocated to each group; but with considering the dropouts, 208 patients were set out to be examined. Statistical analysis was done using IBM SPSS Statistics 25. Continuous variables are described as mean and standard deviation (SD). Categorical variables are described by frequency and percentage. Gender and baseline calf swelling were compared between the four groups using Chi-square. One-way ANOVA analysis was used for comparison of age, BMI, CRP, and D-dimer between the 4 groups. One-way ANOVA analysis was used to investigate the changes in level of CRP, d-dimer, and calf swelling after 3 months. Also post hoc analysis using One-way ANOVA was used to determine the significance of difference between study arms. P value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics of patients

208 patients (52 patients in each group) with unilateral DVT of lower limbs (62.8% right leg) were included in the study (23% had concomitant PTE). During the trial, there were 26 dropouts due to reasons such as death, cancer, and inability to follow up and ultimately 182 patients (50 in Warfarin group, 49 Warfarin + Rosuvastatin, 44 in Rivaroxaban and 39 in Rivaroxaban + Rosuvastatin) finished the trial period (51.64% male). The baseline characteristics of studied patients are shown in Table 1. Among the patients, 54 (29.6%) had DVT in the area above the knee (the popliteal area) and 128 (70.4%) had DVT in the area below the knee. There was no significant difference between the groups in the baseline characteristics at the beginning of the study.

Five patients had iliac involvement (very proximal DVT), two in the Rivaroxaban + Rosuvastatin group and one in each of the other groups (p = 0.28). 42.8% of the patients had CRP above the normal range (6 mg/L) on presentation.

3.2. Outcomes

Table 2 shows the changes in CRP, D-dimer, and calf swelling after 3 months in each study arm. Post hoc analysis of the groups is presented in Table 3 and details are given below:

Occurrence of PTS

Based on the Brandjes score, 31 (17.03%) patients had PTS at the end of the study (table 4). The occurrence of PTS was significantly lower in the groups taking statins (p<0.0001). In addition, no one in the statin groups had severe PTS.

Calf swelling difference > 3 cm

At the beginning of the study 140 (76.9%) patients had more than 3 cm difference in circumference diameter between two legs, 24 (17.1%) of which had differences more than 5 cm. After 3 months of treatment, in 47 (33.5%) patients the difference between circumference diameter of the two calves did not reach normal level (below 2 cm).

Although the change in legs circumference diameter before and after intervention was significant in all groups (p < 0.05), the differences were more prominent in groups 2 and 4 (p < 0.0001). The maximum change of circumference diameter was seen in patients with more than 5cm difference between 2 calves at base and those who were in statin groups.

CRP

Table 1: Comparing the baseline characteristics of patients between groups

Variables	Study groups				P
	1 (n = 50)	2 (n = 49)	3 (n = 44)	4 (n = 39)	
Gender					
Male	27 (54.0)	25 (51.0)	23 (52.3)	19 (48.7)	0.94
Female	23(46.0)	24 (49.0)	21 (47.7)	20 (51.3)	
Age (years)					
Mean ± SD	55.01±4.3	54.04±3.9	56.53±4.4	55.2±4.6	0.06
Body mass index (kg/m2)					
Mean ± SD	30.30±3.2	29.71±3.2	30.09±3.2	30.54±3.3	0.68
CRP (mg/L)					
Mean ± SD	10.73±1.7	8.31±1.6	10.66±2.6	9.53±1.7	0.084
D-dimer (ng/ml)					
Mean ± SD	3034.27±1230.1	3029.86±1471.9	2971.93±1730.8	3664.16±1964.6	0.176
Calf size difference# > 3 cm					
Number (%)	45 (90.0)	37 (75.5)	32 (72.7)	26 (66.7)	0.17
Thrombose location n (%)					
Above the knee	13 (26.0)	16 (32.7)	13 (29.5)	12 (30.8)	0.28
Below the knee	37 (74.0)	33 (67.3)	31 (70.5)	27 (69.2)	

#: Compared with unaffected limb. Data are presented as mean ± standard deviation (SD) or frequency (%).
Group 1: warfarin; group 2: Warfarin + Rosuvastatin; group 3: Rivaroxaban; group 4: Rivaroxaban + Rosuvastatin.
CRP: C-reactive protein.

Table 2: Comparing the studied outcomes before and 3 months after intervention

Variable	Before	After	P value
C-reactive protein (mg/L)			
Warfarin	11.58±8.3	8.35±2.1	0.09
Warfarin + Rosuvastatin	8.53±3.3	2.24±0.4	0.001
Rivaroxaban	11.69±8.6	7.69±3.2	0.07
Rivaroxaban + Rosuvastatin	9.78±4.1	1.62±0.5	0.001
D-dimer (ng/ml)			
Warfarin	3034.27±1230.1	344.54±81.0	<0.0001
Warfarin + Rosuvastatin	3029.86±1471.9	148.48±61.1	<0.0001
Rivaroxaban	2971.93±1730.8	345.33±143.7	<0.0001
Rivaroxaban + Rosuvastatin	3664.16±1964.6	217.83±134.1	<0.0001
Calf swelling difference > 3# cm			
Warfarin	45 (90.0)	23 (4.0)	0.04
Warfarin + Rosuvastatin	37 (75.5)	8 (16.3)	<0.0001
Rivaroxaban	32 (72.7)	11 (25.0)	0.01
Rivaroxaban + Rosuvastatin	26 (66.7)	5 (12.8)	<0.0001

#: Compared with unaffected limb. Data are presented as mean ± standard deviation (SD) or frequency (%).

After 3 months of medication use, serum CRP levels were reduced in all 4 groups of the study but was only significant in groups 2 and 4 (p = 0.001 in both groups). In 11% (20 patients) although the CRP had reduced, it had not reached the normal level (below 6 mg/L).

According to table 3, post hoc analysis revealed that rivaroxaban + rosuvastatin group had more reduction than warfarin + rosuvastatin group (p = 0.84).

D-dimer

After 3 months of treatment, serum D-dimer was reduced in all patients but did not reach the normal level (below 500ng/mL) in 8% of them. Between the patients with the serum D-dimer level above 10000 ng/mL, patients in the statin groups experienced significantly more reduction in D-dimer levels than the other groups. In other words, statins were more efficacious in patients with higher levels of serum D-dimer (p<0.001) Although the mean difference of D-dimer before and 3 months after intervention was statistically significant in all groups, the difference was greater in the rivaroxaban + rosuvastatin vs non-statin groups (p < 0.001) and warfarin + rosuvastatin (p = 0.017).

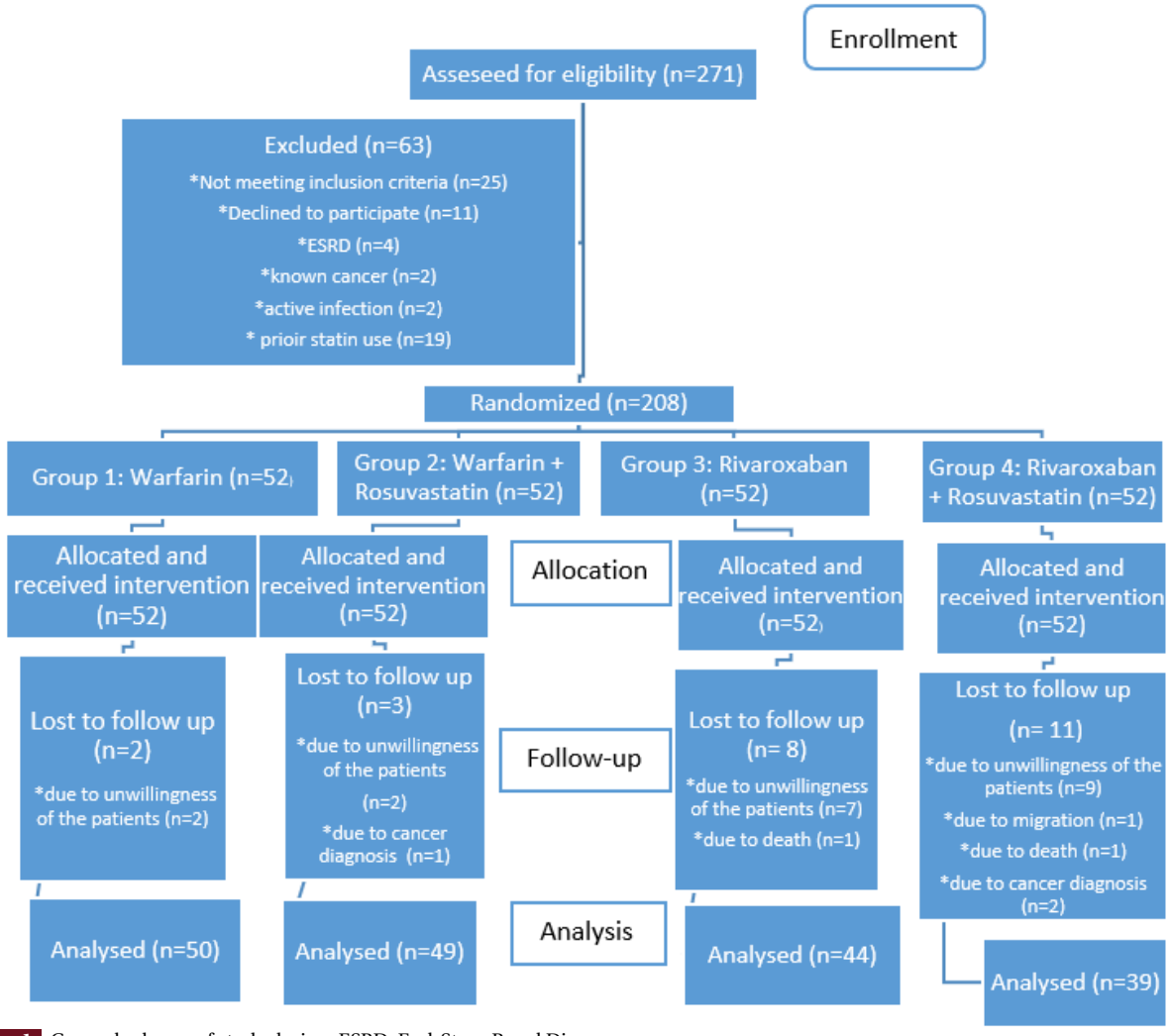

Figure 1: General scheme of study design. ESRD: End-Stage Renal Disease.

4. Discussion

The present study was conducted as a clinical trial with the aim of investigating the effect of the use of statins along with common anticoagulant therapy on the improvement of patients with acute DVT and reduction of PTS incidence.

The results show that the addition of statins to anticoagulants seems to make the regimen more effective in improving the treatment outcomes of DVT patients. Moreover, rosuvastatin administration in combination with rivaroxaban or warfarin significantly reduces the amount of DVT-associated inflammatory factors including CRP and D-dimer, compared to patients receiving anticoagulants alone. It can significantly reduce the incidence of PTS and the difference in the size of the lower limbs within 3 months, which is even more effective when difference between two legs is more than 5 cm.

Statin use was associated with a decreased rate of DVT, PE, or overall VTE in 7 studies (1 randomized clinical trial, 4 case–controlled studies, 1 retrospective cohort study, and 1 basic science study), including the JUPITER trial. The large randomized trial of JUPITER showed that in 17,802 patients, in 26 countries, with a 5-year follow-up, among people with normal LDL-C levels and elevated CRP, rosuvastatin 20mg reduced the risk of VTE by more than 40% compared with placebo (16). In two registrations based on the Danish population, the use of statin among patients with VTE diagnosis was associated with a lower risk of recurrent VTE (hazard ratio (HR)= 0.74, and 95% confidence interval (CI) 0.68-0.87 and 0.72, 95% CI 0.58- 0.88) compared with the group not consuming statin (17). Adjuvant treatment with statins in patients admitted to the hospital with acute PE was also associated with a reduction in the risk of recurrent PE (HR= 0.50, and 95% CI 0.36-0.70) (18). The effect was maintained during and after stopping the anticoagulant therapy. In ad-

Table 3: Post hoc analysis using one-way analysis of variance (ANOVA) to determine the significance of difference between study arms

Variable	Mean difference	P value
Calf swelling difference > 3# cm		
Rivaroxaban+ Rosuvastatin	Reference	-
Warfarin	-1.30342	<0.001
Warfarin +Rosuvastatin	0.73287*	0.06
Rivaroxaban	-1.08360*	<0.001
Change in C-reactive protein level		
Rivaroxaban+ Rosuvastatin	Reference	-
Warfarin	-1.47436*	.003
Warfarin +Rosuvastatin	-0.32620	.864
Rivaroxaban	-1.74709*	.000
Change in D-dimer level		
Rivaroxaban+ Rosuvastatin	Reference	-
Warfarin	-126.70677*	<0.001
Warfarin +Rosuvastatin	69.35699*	0.017
Rivaroxaban	-127.49775*	<0.001
Occurrence of post thrombotic syndrome		
Rivaroxaban+ Rosuvastatin	Reference	-
Warfarin	-1.25562*	0.034
Warfarin +Rosuvastatin	-1.31674*	0.001
Rivaroxaban	-1.03977*	0.044

#: Compared with unaffected limb. *: One-way ANOVA. The difference seems to be significant between the Rivaroxaban-Rosuvastatin group and warfarin alone, or Rivaroxaban alone.

Table 4: Comparing the severity of post thrombotic syndrome (PTS) based on Brandjes score between the 4 studied groups

Severity of PTS	1 (n =50)	2 (n = 49)	3 (n =44)	4 (n =39)	P value
Mild (score ≤ 3)	6 (12.0)	5 (10.2)	4 (9.1)	4 (10.2)	< 0.0001
Moderate (score= 4)	6 (12.0)	2 (4.1)	3 (6.8)	1 (2.5)	
Severe (score ≥5)	4 (8.0)	0 (0.0)	2 (4.5)	0 (0.0)	

Data are presented as frequency (%). Group 1: warfarin; group 2: Warfarin + Rosuvastatin; group 3: Rivaroxaban; group 4: Rivaroxaban + Rosuvastatin.

dition, there was a dose-response relationship in the effect of statin therapy. Interpretation of these effects is however limited due to retrospective nature of the study.

The results of existing studies have been controversial about the effect of rosuvastatin on incidence of PTS. A multicenter randomized controlled pilot trial on 312 patients with acute DVT receiving standard anticoagulation has shown that the addition of rosuvastatin 20 mg once daily for 180 days, does not significantly decrease PTS incidence (19). On the other hand, similar to our results, a randomized controlled trial including 230 patients with DVT, reported the reduction of PTS incidence following rosovastatin administration. The results did not show significant differences in D-dimer levels following rosuvastatin administration in addition to low molecular weight heparin (LMWH); but patients who had received statin had significantly lower levels of CRP and showed a significant decrease in PTS incidence after 3 months of follow-up (11). In confirmation of these findings, various studies have shown that statin therapy, can reduce the level of plasminogen activator inhibitor-1 (PAI-1) as a fibrinolytic inhibitor and the level of tissue factor as a coagulation cascade initiator (20, 21). Decrease in the level of PAI-1 or TF alone can increase net intravenous and intra-arterial clot fibrinolysis (22). The inhibitory mechanism of statins on TF consists of inhibiting synthesis of the isoprenoid mediator and in vitro inhibition of geranylgeranylation in the Rho / Rho kinase pathway (23). Reducing the activation of the Rho family reduces the expression of one of the key transcription factors called NF-KB; this transcription factor induces positive TF regulation. In addition, statins increase the expression of kruppel like factor 2 (KLF2), a positive regulator of eNOS and thrombomodulin, and an inhibitor of TF and PAI-1 (24). Clinical and experimental studies also show that statins inhibit the activation of cyclooxygenase 1 (COX-1) and enhance the activity of nitric oxide synthase (NOS), thereby reducing the activation and accumulation of platelets (25).

Results of this study also suggest a stronger protective effect against VTE with rivaroxaban compared with warfarin. The effect of rivaroxaban on D-dimer levels was mentioned in other studies as well (26). Rivaroxaban, as an inhibitor of

factor Xa, disrupts the intrinsic and external pathways of coagulation cascade, and ultimately inhibits the formation of thrombin, subsequent fibrinolysis, and the production of D-dimer (27). D-dimer not only acts as an indicator of thrombotic activity, but also correlates to the size and the burden of the thrombosis (28). Due to the 8-hour half-life of D-dimer (25), reduction of D-dimer levels during the first 24 hours of drug therapy is expected. Similar effects was seen with other anticoagulants, including heparin, warfarin and apixaban (27). However, data seems to be more robust for rivaroxaban. In a study by Utne et al., rivaroxaban showed an absolute 14% reduction of PTS two years after an acute DVT episode and also improved quality of life compared to treatment with warfarin. It was suggested that the effect of rivaroxaban on PTS is related to its rapid time to peak concentration and its stable anticoagulation effect. Rivaroxaban's other properties such as its binding and inhibition of the thrombus bound factor X can also be involved in this effect (29). Another suggested mechanism is the involvement of residual vein thrombosis as a main factor in the development of PTS. In a study by Prandoni et al., residual vein thrombosis formation in patients with proximal DVT was compared between direct oral anticoagulants (DOACs) and vitamin K antagonists (VKAs) after three and/or six months. DOACs showed more protective effect against residual vein thrombosis compared with VKAs (41% and 21% after 3 and six months respectively, vs 52.3% and 54.5%) (30).

In another study by Cheung et al., rivaroxaban showed a numerically lower but statistically non-significant risk of PTS compared to enoxaparin/VKA treatment in acute DVT patients. Non adherence when using VKAs was suggested as the main reason for better long term clinical outcomes regarding PTS when using rivaroxaban compared to VKAs (31).

Regarding controversial results of studies on rosuvastatin adjuvant therapy, the anticoagulant used for the treatment may affect the incidence of PTS. The results of our study show a more significant difference for PTS incidence between the administration of rivaroxaban+rosuvastatin with warfarin alone or warfarin+rosuvastatin compared to rivaroxaban alone; which may propose the hypothesis of the synergistic effect of rivaroxaban and rosuvastatin for PTS prevention.

5. Limitations

The strength of our study is that besides investigating the effect of rosuvastatin, the effect of two types of anticoagulants with and without rosuvastatin was. So far, no study has investigated the effect of rosuvastatin alongside rivaroxaban and compared rivaroxaban and warfarin in this context. Our study has several limitations. First, the trial was not aimed to study the effects of rivaroxaban. Second, a single ultrasound sonographer was used for sonography, therefore having a second opinion might change results. Third, the same brand of rosuvastatin was used for all groups (Rosurexin, Actoverco), the issue of bias in the results can be raised, of course, the pharmaceutical company had no involvement in the study and interpretation of the results, and only supplied the drug.

6. Conclusion

The addition of rosuvastatin to anticoagulants seems to be effective in improving the treatment outcomes of DVT patients. Rosuvastatin administration in combination with rivaroxaban or warfarin significantly reduces the level of inflammatory factors including CRP and D-dimer, compared to patients receiving anticoagulants alone. Furthermore, it can significantly reduce the incidence of PTS and the difference in the size of the lower limbs within 3 months.

7. Declarations

7.1. Acknowledgments

We would like to thank ACTOVERCO Pharmaceutical Factory, Karaj, Iran for supplying rosuvastatin for participants.

7.2. Conflict of Interest Statement

For decreasing the risk of potential bias ACTOVERCO Pharmaceutical Factory had no involvement in the study and interpretation of the results, and only supplied rosuvastatin.

7.3. Fundings

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7.4. Authors' contribution

MP and RB: designed the study. RL and ZT: collected the data. KKT drafted the manuscript and edited final manuscript. All authors have read and approved the manuscript.

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