

# Can deep vein thrombosis be predicted after varicose vein operation in women in rural areas?

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## Abstract

**Introduction.** Chronic venous disease is a group of symptoms caused by functional and structural defects of the venous vessels. One of the most common aspects of this disease is the occurrence of varicose veins. There are many ways of prevention and treatment of varicose veins, but in Poland the leading one is still surgery. As in every medical procedure there is the possibility of some complications. One of them is deep vein thrombosis (DVT). The diagnosis of DVT can be difficult, especially when access to a specialist is limited, such as in case of rural patients.

**The aim of the study.** The aim of the study was estimation of the influence of LMWH primary prophylaxis on the formation of postoperative DVT, as well as sensitivity and specificity of clinical examination and D-dimer value in diagnosis of postoperative DVT in women.

**Materials and methods.** The study was conducted in a group of 93 women operated on in the Department of General, Vascular Surgery and Angiology at the Karol Marcinkowski University of Medical Sciences in Poznań, Poland. The patients had undergone a varicose vein operation and were randomly divided into two groups: A – 48 women receiving LMWH during two days of the perioperative period, B – 45 women receiving LMWH during seven days of the perioperative period.

**Results.** There was no significant difference in the postoperative DVT complications in both groups. The value of D-dimer > 0.987 mcg/ml and swelling > 1.5 cm of shin (in comparison to the preoperative period) plays a significant role in diagnosis of DVT.

**Conclusions.** The extended primary prophylaxis with LMWH does not affect the amount or quality of thrombotic complications after varicose vein operation. If the DVT occurs, the evaluation of the D – dimer and careful clinical examination can be a useful method for its diagnosis.

## Key words

varicose veins, postoperative DVT, surgery

## INTRODUCTION

Chronic venous disease (CVD), together with its consequences, is one of the oldest diseases of the human race, since – according to one theory – man assumed the erect position. [1]. The essence of disease are congenital or acquired abnormality in blood outflow from the lower limbs, in most cases caused by incompetent valves. This venous hypertension leads to morphological and structural lesions in the vein wall and surrounding tissues which are manifested by varicose veins, skin changes and venous ulcers. CVD generates costs for its treatment and affects the quality of life, as well as being associated with the loss of ability to work. [2, 3, 5]. Varicose veins are one of the most common manifestations of CVD. In developed countries, the disease affects nearly every second person over 40 years of age, with an advantage of female (40–60%) over men (25–30%). One year incidence of CVD is 2.6% for women and 1.9% for men [7]. Varicose veins can be divided into primary and secondary. The causes of primary varicose veins are still unrecognized, although family inheritance is one of its causes [8]. Other well known risk factors are: age, gender, pregnancy, sedentary lifestyle and obesity [9].

There are many ways of treating CVD, but surgery and compression therapy play a leading role. The pressure reduces the lumen of the vein and restores valve function, reduces the volume of venous reflux, and normalizes the morphological changes in the vein wall [10]. Systematic application of pressure improves the patients' quality of life [11, 12, 13, 14]. Pharmacological treatment is supportive for basic treatments such as compression therapy and surgery. Phlebotrophic medications are effective in many ways as they increase venous tone by noradrenergic activity, protect the venous endothelium against hypoxia, reduce the adhesion of leukocytes to the endothelium and valves, and improve the permeability of the capillaries and lymphatic drainage [15, 16, 17, 18, 19, 20, 21].

Surgical treatment aims primarily to eliminate the causes of hypertension in the superficial venous system, which usually means operating on the first incompetent valve on the border of the deep venous system. Treatment usually involves two aspects:

1. crosssection and stripping of the great (GSV) and/or small saphenous vein (SSV);
2. Miniphlebectomy.

Potential complications after surgery of varicose veins include: bleeding requiring reoperation, arterial or vein injuries, neurological disturbance (foot-drop), haematomas, abnormal sensation (touch), leakage of lymph from the

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groin, infection, deep vein thrombosis (DVT), and recurrent varicose veins.

DVT of the lower limbs is one of the most serious complications of varicose veins after surgery. The result is the occurrence of the thrombus in the vein and potential risk of serious complications, such as: pulmonary embolism (and as a consequence, pulmonary hypertension, heart failure or death), post-thrombotic syndrome of secondary varicose veins. There are many others risk factors of DVT, some are related to smoking, and the smoking rate in Poland still remains very high [22]. The diagnosis of DVT after surgery often poses a big problem as the disease in most cases is asymptomatic.

**Objectives.** The aim of the study was to estimate the influence of low-molecular-weight heparin (LMWH) primary prophylaxis on formation of postoperative DVT, as well as the sensitivity and specificity of clinical examination and D-dimer value in the diagnosis of postoperative DVT in women.

## MATERIALS AND METHOD

The study was conducted in a group of 96 women with CVD scale C2-C6 according to the CEAP classification hospitalized in Department of General, Vascular Surgery and Angiology at the Karol Marcinkowski University of Medical Sciences in Poznań, Poland. The study was prospective and randomized. Permission was granted by the Bioethical Committee of the University.

Patients were randomized into two groups: Group A – on the day before surgery the patients were given enoxaparin 40 mg, and 40 mg enoxaparin sc on the day of the operation, 24 hours after the first dose. Group B – on the day before the surgery patients were given enoxaparin 40 mg, and 40 mg enoxaparin sc on the day of operation, 24 hours after the first dose. Then, enoxaparin was administered at a dose of 40mg/day sc until the 7<sup>th</sup> day after surgery.

After admission to hospital, all patients parameters necessary were tested for the operation and D-dimers. The next day, the surgery was performed and D-dimers tested. All patients were operated on by the same surgeon. In all cases, one lower limb was operated on.

The day after the surgery all patients were discharged home where from days 2–28, reporting for control test at the Department on the 7<sup>th</sup> and 28<sup>th</sup> day.

**Table 1.** Characteristics of studied groups

	Group A	Group B	p-value
Age (years)	50.50 ± 13.17	51.82 ± 9.23	p=0.578
Mean duration of disease (years)	9.89 ± 4.80 Median 9 min. 2 – max. 25	9.76 ± 3.59 Median 9 min. 2 – max. 17	p=0.8340
Reflux in GSV according to Hach classification	III – 20 IV – 36	III – 27 IV – 28	p=0.403
D-dimer value before surgery (mcg/ml)	0.271 ± 0.128	0.268 ± 0.134	p=0.922
BMI	24.47 ± 2.05	24.66 ± 1.85	p=0.635

GSV – Great saphenous vein. BMI – Body mass index

Inclusion criteria:

1. insufficiency of the great saphenous vein (III or IV degree) and varices of lower limb;
2. lack of acute or chronic DVT in colour Doppler imaging;
3. baseline D-dimer value normal;
4. presence of 1 – 2 insufficient perforating veins;
5. female over 18 years of age;
6. good general condition of the patient;
7. ability to provide written informed consent.

Exclusion criteria:

1. chronic treatment with an anticoagulant drug;
2. chronic treatment with venoactive drugs (VADs);
3. insufficiency of GSV (I or II degree);
4. insufficiency of SSV;
5. recurrent varices after surgery (REVAS);
6. patient with active cancer;
7. lymphatic oedema;
8. women who are pregnant or breast feeding;
9. presence of 2 or more DVT risk factors, excluding varicose veins;
10. presence of skin infection;
11. history of DVT, haemorrhagic diathesis, heparin induced thrombocytopenia (HIT);
12. ankle-brachial index (ABI) < 0.8.

In the study participated:

- group A – 50 women;
- group B – 46 women.

Doppler ultrasonography examination was performed with a LOGIQ P5/A5 device.

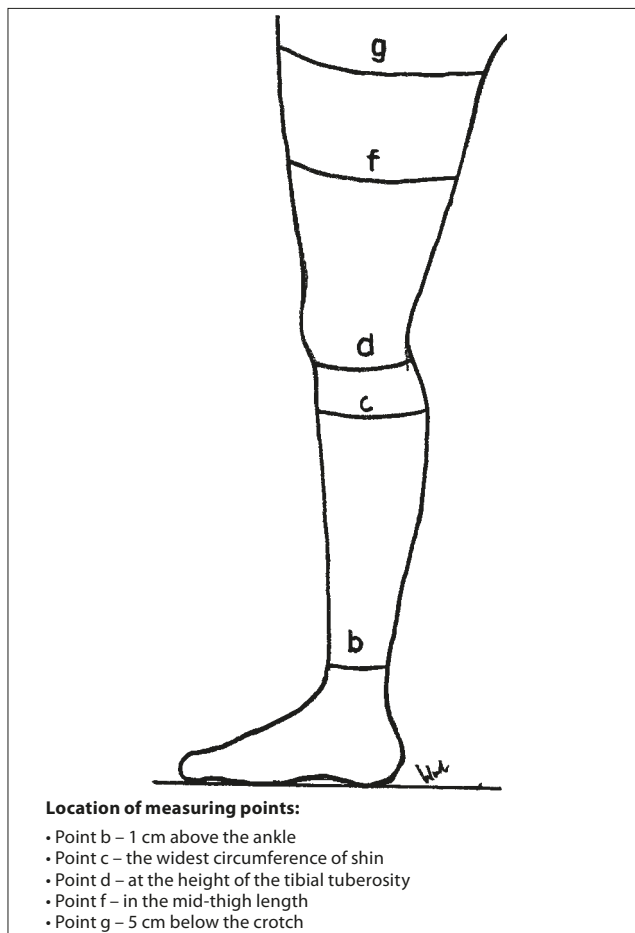
The presence of postoperative DVT was evaluated at the following levels:

1. over the medial ankle (posterior tibial veins, anterior tibial and peroneal veins, part of GSV left after stripping);
2. widest circumference of the shin (SSV, part of GSV left after stripping);
3. popliteal area (SSV, popliteal vein);
4. mid-thigh length (femoral vein);
5. inguinal area (femoral vein);
6. abdominal cavity (iliac vein).

D-dimers concentration in blood serum was determined by immunoturbidimetric test using Tina-quant (Roche Diagnostics) on a Hitachi 902 analyzer. Reference value was the concentration of D-dimer 0 – 0.5 mcg/ml (Figure 1).

**Statistical analysis.** Performed using the MedCalc statistical tests ver.11.01.0 and GraphPad Prism 5. For the value expressed on the interval scale, the mean and standard deviation were calculated. In order to verify the compliance of normal distribution, the Kolmogorov-Smirnov and Shapiro-Wilk tests were applied, and equality of variance was tested by Fisher's and Levene's tests. After fulfilling the above conditions, the Student's *t*-test was applied. In the case of non-compliance with normal distribution for an interval scale (unpaired variables model) and ordinal scale, the U Mann-Whitney test was used; in this case, the median was also calculated. In the case of non-compliance with the normal distribution of variables in the paired variables model, the Wilcoxon test was used.





**Figure 1.** Schematic representation of the points on the limb at which circumference measurements were made

Comparing data expressed in the nominal scale was possible by using the  $\chi^2$  test with Yates's correction, and – in the case of a small number expected – Fisher's exact test. For some parameters, sensitivity, specificity, PPV, NPV, LR and ROC curves drawn. Testing the statistical significance was conducted with the  $P=0.05$  confidence level.

## RESULTS

The study was randomized and had a single-blind nature, and comprised 96 women who were randomly divided into 2 groups.

Two women in Group A failed to attend an appointed visit on the 28<sup>th</sup> day of the test, and were therefore excluded from the observation. One woman from Group B had a decreased level of platelets after administering LMWH, and it was therefore decided to discontinue use of the medication. The patient had no symptoms of platelet disorders and the level of platelet quickly returned to normal. This woman was excluded from the statistical analysis.

Taking the above into consideration, the study involved accordingly:

Group A – 48 women;

Group B – 45 women.

Deep venous thrombosis occurred in both groups in 5 cases, representing 4.65% of patients. In the study, all the cases of thrombosis were diagnosed at the visit on the 7<sup>th</sup> day.

In order to assess the usefulness of D-dimer and clinical examination in diagnosis of postoperative DVT, the studied population was divided into 2 groups: patients who developed postoperative DVT (Group C) and patients in whom the disease did not occur (Group D).

**Table 2.** Change in average value of D-dimer in group of patients with and without DVT

Change in the average value of D-dimer in groups of patients with DVT (group C) and without DVT (group D) in the perioperative period (value of D-dimer in mcg / ml)				
Group	Day - 1	Day 0	Day 7	Day 28
DVT (group C)	0.256 ± 0.200	0.473 ± 0.666 Median 0.140 min. 0.000 – max. 1.625	2.534 ± 1.336 Median 2.116 min. 1.034 - max. 4.155	2.004 ± 1.876 Median 1.340 min. 0.447 – max. 5.112
Without DVT (group D)	0.270 ± 0.127	0.423 ± 0.202 Median 0.400 min. 0.880 – max. 1.411	0.663 ± 0.877 Median 0.404 min. 0.108 – max. 5.859	0.482 ± 0.525 Median 0.368 min. 0.025 – max. 3.258
p-value	p = 0.815	p = 0.657	p < 0.0001	p < 0.0001
Statistical test	The unpaired samples Student's t-test	Mann-Whitney U test	Mann-Whitney U test	Mann-Whitney U test

**Table 3.** Sensitivity, specificity, PPV, NPV, LR with respect to D-dimer in the detection of postoperative DVT

Sensitivity, specificity, PPV, NPV, LR for D-dimer in diagnosis of postoperative DVT in the group with DVT (group C) and without DVT (group D)			
sensitivity	100%	PPV	16%
specificity	70%	NPV	100%
LR 3.33			

PPV – positive predictive value; NPV – negative predictive value; LR – likelihood ratio

In addition to assessing D-level of D-dimer in the detection and prediction of postoperative DVT, changes in limbs circumferences on days -1 and +7 in Groups C and D were also analyzed.

**Table 4.** Comparison of average limb circumference on days -1 and +7 in groups with and without DVT

Comparison of the average operated limb circumferences for days -1 and 7 in patients with DVT (cm) (Group C)					
Location of measuring points	Day -1	Day +7	The average change in circumference	p-value	Statistical test
B	23.5	23.8	+0.3	p=0.2080	The paired samples Student's t-test
C	38.6	40.5	+1.9	p=0.0005	
D	36.3	37.4	+1.1	p=0.0743	
F	51.5	52.8	+1.3	p=0.1216	
G	61.9	62.1	+0.2	p=0.3739	
Comparison of the average operated limb circumferences for days -1 and +7 in patients without DVT (cm) (Group D)					
Location of measuring points	Day-1	Day+7	The average change in circumference	p-value	Statistical test
B	24.0	24.3	+0.3	p=0.0793	Wilcoxon signed-rank test
C	38.0	38.8	+0.8	p=0.0006	
D	36.0	36.6	+0.6	p<0.0001	
F	52.8	52.3	-0.5	p=0.5455	
G	62.9	61.5	-1.4	p=0.0075	

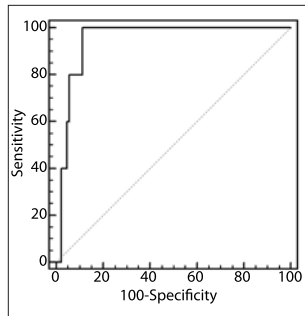
Based on the results of D-dimer and the changes of circumference measured at different points of the operated limb – by using ROC curve – the optimal cut-off values for the examined parameters in the diagnosis of postoperative DVT were determined.

**Table 5.** Result of ROC curve analysis

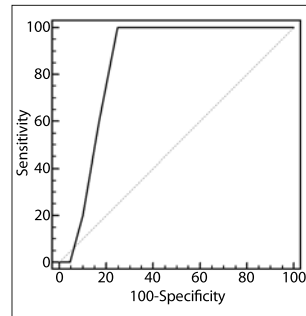
Receiver operating characteristic curve analysis result						
The tested parameter	AUC	95% confidence interval	Highest sensitivity	Highest specificity	Result	p-value
D – dimer	0.948	0.881–0.983	100	88.6	>0.987	0.0001
Rb	0.574	0.467–0.676	100	13.6	<= 0	0.4627
Rc	0.847	0.757–0.913	100	75.0	<= -1.5	0.0001
Rd	0.600	0.493–0.700	60	71.6	<= -1.5	0.498
Rf	0.689	0.584–0.781	40	85.2	<= -2	0.1057
Rg	0.583	0.476–0.684	100	28.4	<= 0	0.3002

**Abbreviations:**

Rb – difference in circumference at height 'b' in days -1 and +7  
 Rc – difference in circumference at height 'c' in days -1 and +7  
 Rd – difference in circumference at height 'd' in between -1 and +7  
 Rf – difference in circumference at height 'f' in between -1 and +7  
 Rg – difference in circumference at height 'g' in between -1 and +7  
 AUC – Area Under Curve



**Figure 2.** ROC curve for D-dimer value measured on day 7



**Figure 3.** ROC curve for the difference in circumference measured on days 1 and 7 at height 'c'

## DISCUSSION

Varicose veins of the lower limbs are one of the most common diseases of the developed countries. According to the National Health Institute, 20,508 urban area inhabitants (5,987 men and 1,4521 women) and 11,500 rural area inhabitants (3,181 men and 8,319 women) were hospitalized due to this disease in 2011. Average duration of hospitalization was 2.7 days and was higher for rural residents (3.1 vs. 2.6 days). Despite the development of endovascular and obliteration methods, the Babcock-Mueller operation remains the most common surgery in the treatment of varicose veins in Poland. The procedure itself is simple, but is not free of complications, which in some cases can be fatal (pulmonary embolism) or may cause long-term serious consequences (such as post-thrombotic syndrome). This study did not present the efficacy of the prolonged model of thromboprophylaxis prevention (group A – 3 cases DVT, group B – 2 case,  $p=1.0$ ). DVT is still a rarely diagnosed disease; however awareness is increasing year-by-year. Where the patient is concerned, it is better to diagnose and treat as DVT, even though it is not present, than to overlook the already existing disease. The best way to identify the disease is to conduct the Doppler test, the availability of which in Poland is still far from the satisfactory. Another effective way of diagnosis is phlebography – an invasive procedure, and even less available.

In the presented study, the attempt was undertaken to determine an effective way to identify DTV after the operation, based on the clinical examination and D-dimer levels in blood serum. These procedures can be performed in any doctor's surgery. According to manufacturer specification, the test used to examine D-dimers is highly sensitive in DTV detection – 99%; specificity unfortunately is only 45.8%, PPV – 42%, and NPV – 99.4%. It is known that stripping and phlebectomy are processes that can activate coagulation and fibrinolysis. Böhler et al. observed a change in the thrombin-antithrombin (TAT) complex, fragments 1 and 2 of prothrombin and D-dimers after the stripping of GSV and in the control group [23]. The study showed a statistically significant increase in all 3 parameters in the group of patients after the stripping, due to the saphenous vein failure, in comparison to the control group. Hinterhuber et al. showed a statistically significant increase in TAT, TTP, D-dimer, plasmin –  $\alpha$ 2- antiplasmin complex, and plasminogen activator inhibitor, compared to the baseline in the group of patients after removal of the saphenous vein [24]. There was no statistically significant difference in the level of tissue plasminogen activator, prothrombin fragment F1+2 and plasminogen activator inhibitor (PAI-1).

In the presented study, the sensitivity of D-dimer in the diagnosis of DVT was 100% and specificity up to 70%. These results relate to day 7, when all the cases of DVT were diagnosed. It should be noted that in each group (i.e. C and D) an increase of D-dimer was observed on day 7, but mean values for patients with DVT were much higher (Tab. 2). D-dimers PPV was only 16% and NPV 100%. Based on the frequency table (Tab. 3), the usefulness of D-dimer for the determination of post-operative DVT can be inferred, and thus determine the likelihood ratio (LR), which is 3.33. This result indicates that the patient with DVT is 3.3 times more likely to have oversized D-dimer levels than patients who do not have DVT. The relationships of oedema on the 1<sup>st</sup> and 7<sup>th</sup> day were analyzed in detail, since all cases of DVT were diagnosed on the 7<sup>th</sup> day. Interestingly, in the group of women with DVT, there was an increase in oedema measured in each of the levels, the largest (1.9 cm) was located in the widest point of the shin. In the group of patients who did not develop DVT, statistically significant difference concerned shin swelling, and it was always an increase in the circuit. However, the average thigh circumference of the operated limb did change significantly 5 cm below the crotch, although the absolute value was reduced, even up to 1.4 cm, which may prove to be a valuable indication of the effectiveness of the postoperative compression therapy. The lack of such efficacy can, in turn, give rise to the suspicion of DVT, as evidenced by the increase in the average circumference in the group with postoperative DVT.

The results obtained in the presented study lead to the conclusion that accurate measurements of the limb circumference before and after the treatment enables the selection of a group of patients with DVT. It should also be noted that superficial thrombophlebitis can cause oedema and increase in D-dimer. In order to evaluate the usefulness of measuring the circumference of the operated leg and determination of D-dimer, and to select the optimal cut-off value, ROC curves were drawn. ROC analysis showed that the highest sensitivity and specificity value of D-dimer is 0.987 $\mu$ g/ml (sensitivity 100%, specificity almost 90%) (Fig. 2), and the measurement circumference at point 'c' (sensitivity

100%, specificity almost 75%) in which the obtained measure is  $\geq 1.5$  cm (Fig. 3). Measurements made at other levels did not contribute to the potential diagnosis or even the suspicion of DVT (Tab. 5).

Pączkowska [25] analyzed the availability of the services of doctors and specialists important from the point of view of identifying DVT. Although the negative assessment of the availability of a specialist surgeon in 2004 amounted to only (or as much as) 25%, it can hardly be described as an optimal situation. This is due to the fact that almost none of the general surgeons have the experience and skills to detect or exclude postoperative thrombosis using Doppler examination. Also, the delay in waiting for a visit to a specialist within national health insurance coverage is, at least, a few days, while the waiting time for an appointed visit to a specialist in vascular surgery is at least several weeks. For a patient with DVT, such a wait could be fatal. Another common obstacle is the limitation of services for a given period. Selecting a surgery of a private medical specialist varies according to the financial circumstances, although education and the place of residence can also have an impact. Among patients using private medical services, 56% came from among the rural population, 65% of the urban population from towns up to 20,000 inhabitants, and 54% from cities with 20,000–100,000 inhabitants. An important limitation in seeking treatment in the private sector is the patient's financial status. Almost  $\frac{1}{4}$  of surveyed patients stated that they had not undertaken the treatment over the year due to this reason. This most often concerned pensioners, people with primary education, the unemployed and the elderly.

To conclude with a simple physical examination and determination of D-dimer, each doctor is able to select a group of women with a high probability of DVT, which enables the implementation of treatment, and thus prevents the potential impact of the disease. This is most important in the case of rural women whose access to a specialist is worse than in urban area. In such cases, a general physician (GP) may diagnose and treat DVT according to well known standards.

## CONCLUSIONS

Increase in the circumference of the operated limb at each measurement point and the widest point of the shin  $>1.5$  cm, compared with the preoperative measurement and the levels of D-dimers  $> 0.987$  mcg/ml, allow a highly probable diagnosis of DVT. In the presented study, the sensitivity of D-dimer in the diagnosis of DVT was 100%, as was the specificity, therefore the ability to detect the really healthy persons up to 70%. These results refer to day 7 after the operation on which all cases of thrombosis were diagnosed.

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