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Chronic thrombotic scarring in patients with acute deep venous thrombosis of the lower limbs

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Abstract

Some patients with acute deep venous thrombosis of the lower limbs may present risk factors for recurrent disease. **Aims:** To analyze the most important conditions related to recurrent deep venous thrombosis of the lower limbs, other than thrombophilias. **Patients and methods:** We examined 88 consecutive patients (47 males-53.41%, average age 64.9±13.9 years) admitted to a Medical Clinic in 2007. Duplex ultrasonography was performed to assess acute deep venous thrombosis and post-thrombotic syndrome. Anamnesis and physical examination were used to detect risk factors for recurrent disease. The 28 subjects with acute deep venous thrombosis and post-thrombotic syndrome were included in group A (31.82%). Group B comprised 60 patients (68.18%) with acute deep venous thrombosis without post-thrombotic syndrome. **Results:** Risk factors for recurrent disease in groups A and B were the following: personal history of deep venous thrombosis of the lower limbs (17 subjects versus 7, p<0.0001), varicose veins (14 vs 24, p=0.51), obesity (13 vs 18, p=0.21), malignancy (6 vs 8, p=0.25), chronic obstructive lung disease (5 vs 6, p=0.24), prolonged immobilization (1 vs 7, p=0.21), major surgery (1 vs 1, p=0.54), stroke (0 vs 3, p=0.62), family history of deep venous thrombosis, immobilizing plaster cast, and congestive heart failure (0 vs 1, p=0.54). Location of thrombi in patients in groups A and B was as follows: 18 patients in group A vs 25 subjects in group B on the left side and 13 patients in group A vs 20 patients in group B on the right side (p=0.02). **Conclusion:** Post-thrombotic syndrome correlated with personal history of deep venous thrombosis and previous deep venous thrombosis located in the left lower limb.

Keywords: deep venous thrombosis, post-thrombotic syndrome, recurrence, risk factors for thrombosis

Rezumat

Unii pacienţi cu tromboză venoasă profundă acută a membrelor inferioare pot prezenta factori de risc pentru apariţia recurenţelor. **Obiectiv:** Ne-am propus să studiem cele mai importante condiţii legate de recurenţa trombozei venoase profunde, altele decât trombofilia. **Pacienţi şi metodă de lucru:** Am examinat 88 de pacienţi consecutivi (47 bărbaţi-53,41%, vârstă medie de 64,9±13,9 ani) internaţi într-o clinică medicală în anul 2007. Ultrasonografia duplex a fost folosită pentru stabilirea diagnosticului trombozei venoase profunde acute şi al sindromului posttrombotic. Anamneza şi examenul obiectiv au permis identificarea unor factori de risc pentru apariţia recurenţelor. Cei 28 de subiecţi cu tromboză venoasă profundă acută şi sindrom posttrombotic au format grupul A (31.82%), iar cei 60 de pacienţi cu tromboză venoasă profundă acută fără sindrom posttrombotic au format grupul B (68.18%). **Rezultate:** Factorii de risc pentru apariţia recurenţelor, la pacienţii din grupurile A şi B, au fost următorii: antecedentele personale de tromboză venoasă profundă (17 subiecţi versus 7, p<0,0001), boala varicoasă (14 vs 24 de pacienţi, p=0,51), obezitatea (13 vs 18, p=0,21), cancerul (6 vs 8, p=0,25), bronhopneumopatia obstructivă cronică (5 vs 6, p=0,24), imobilizarea prelungită la pat (1 vs 7, p=0,21), operaţiile majore (1 vs 1, p=0,54), accidentul vascular cerebral (0 vs 3, p=0,62), antecedentele trombotice familiale, imobilizarea gipsată şi insuficienţa cardiacă congestivă (0 vs 1, p=0,54). Localizarea trombilor a fost următoarea: la nivelul membrului inferior stâng, la 18 bolnavi din grupul A şi la 25 pacienţi din grupul B şi la nivelul membrului inferior drept, la 13 bolnavi din grupul A şi la 20 pacienţi din grupul B (p=0,02). **Concluzie:** Prezenţa sindromului posttrombotic s-a corelat cu antecedentele personale patologice trombotice şi cu localizarea trombozei venoase profunde acute la nivelul membrului inferior stâng.

Cuvinte cheie: tromboză venoasă profundă, sindrom posttrombotic, recurenţă, factori de risc pentru tromboză

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Introduction

Venous thromboembolism is defined by the existence of deep venous thrombosis (DVT) and/or pulmonary embolism. There are many environmental or acquired risk factors (RF) associated with the development of DVT [1,2]. These factors are classified into three categories: strong, moderate and weak. Fractures, hip or knee replacements, major surgery and major trauma are strong

RF - odds ratio (OR) greater than 10. Moderate RF (OR 2-9) include personal history of thromboembolism, thrombophilia, cancer, chemotherapy, paralytic stroke, congestive heart failure, respiratory failure, arthroscopic knee surgery, oral contraceptives, hormone replacement therapy, and postpartum period. Some diseases and conditions are weak RF such as increasing age, immobility, obesity, laparoscopic surgery, varicose veins, and antepartum period [3].

Post-thrombotic syndrome (PTS), recurrence of thrombosis and pulmonary embolism are the main complications of DVT [4]. The following modifications of the deep veins characterize the PTS: thickened wall, decreased caliber, nonocclusive intraluminal material (thrombus), and reflux [5,6].

In many cases, older thrombi and deep-vein reflux are detected by ultrasonography in patients with clinical suspicion of acute DVT. Recurrence depends on predisposing factors (e.g. personal history of thromboembolism, cancer and inherited blood clotting diseases as moderate RF) so re-thrombosis may occur in subjects with PTS [7-9].

Aims

We investigated the major diseases and conditions (location of thrombi and predisposing factors for venous thromboembolism other than thrombophilias) associated with recurrent thrombosis.

Patients and methods

This study was conducted at the Internal Medicine Department of the Municipal Hospital „Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, Romania between January and December 2007. The study protocol was approved by the local Ethics Commitee.

The algorithm for diagnosis of DVT was based on the determination of pre-test probability of DVT, D-dimer test and compression ultrasonography [10]. Predicting pre-test probability means the calculation of the Wells' score by adding the points given to different clinical characteristics and by subtracting two points if there is an alternative diagnosis such as Baker's cyst. The main clinical characteristics which are awarded one point are swelling of the whole leg, personal history of DVT, collateral non-varicose superficial veins, plaster immobilization, paralysis, bed rest more than three days, and active cancer. Possible score is between -2 and 9. Score of 2 or higher means that DVT is likely. Thrombosis is unlikely if the score is less than 2. Compression ultrasonography was performed in patients with score greater than or equal to 2 and in those with score less than 2 associated with positive D-dimer test [10-12].

The main ultrasound criterion for detecting acute DVT was the lack of compressibility in at least one deep vein. Other acute DVT criteria were: increased cross-sectional diameter, absence of Doppler signal and collateralization. Thickened venous wall, decreased cross-sectional diameter, small echogenic thrombus and valvular insufficiency characterized the PTS [5,13].

We used two duplex ultrasound machines: General Electric Logiq 500 with a 7.5 MHz linear transducer and Aloka Prosound SSD 4000 equipped with a linear transducer with variable frequency between 7 and 10 MHz.

A total of 88 consecutive inpatients met the inclusion criteria for this study. Depending on the presence of PTS and DVT criteria patients were divided into two groups: A (acute DVT patients with known or unknown PTS) and B (DVT subjects without PTS).

Following parameters were analyzed in all patients: demographic data (gender, age), anamnestic data (personal history of DVT, laparoscopic or major general surgery, arthroscopic knee surgery, malignancy, chemotherapy, bed rest of more than three days, hormone replacement therapy, oral contraceptives, and pregnancy), physical exam data (obesity, varicose veins, stroke, respiratory insufficiency, congestive heart failure) hematologic tests (complete blood count, coagulation, D-dimer test), biochemical tests (fasting blood glucose and lipid profile, serum creatinine), morphological data (thrombus location, echogenicity and caliber, venous wall thickness and compressibility and collateralization) and functional data (spontaneous flow, Valsalva response, augmentation, reflux).

Venous system of the lower limbs was analyzed bilaterally on segments: inferior vena cava and iliac veins, femoral veins (common, superficial and deep), popliteal vein and calf veins (posterior tibial, peroneal and anterior tibial veins, gastrocnemius and soleal veins).

We performed an observational transversal study. Statistical analysis was done using Epi Info computer package, version 3.3.2. We performed univariate analysis (χ^2 test, ANOVA test with a p-value less than 0.05 as selected level of statistical significance) and logistic regression (to characterize parameters related to location of thrombi when p-value was less than 0.10 in univariate analysis)

Results

Eligible patients age was between 23 and 86 years (mean 64.9±13.9 years). Patients' distribution by age was as follows: under 40 years (10 – 11.4%), 41-59 years (22

– 25%), 60 – 74 years (34 – 38.6%) and over 75 years (22 – 25%). There were 47 men (53.4%) and 41 women (46.6%).

Some RF were encountered in many patients: varicose veins (38 subjects – 43.1%), obesity (31 patients – 35.2%), personal history of DVT (24 – 27.2%), cancer (14 – 15.9%), respiratory failure (11 – 12.5%) and bed rest more than three days (8 – 9%).

We found 183 occluded venous segments in the 88 patients included in our study: tibioperoneal (49 – 55.6%), soleo-gemelar (47 – 53.4%), popliteal (39 – 44.3%), femoral (38 – 43.1%) and iliac (10 – 11.3%).

Thrombi location was in the left lower limb in 43 cases (48.8%) and in the right lower extremity in 33 subjects (37.5%). Only 12 patients (13.7%) had bilateral thrombosis.

Chronic thrombotic scarring and deep vein reflux were found in 28 patients (31.8%) with acute DVT criteria.

The figures 1-3 illustrate the acute DVT diagnosis while the figures 4-7 present the changes encountered in the PTS.

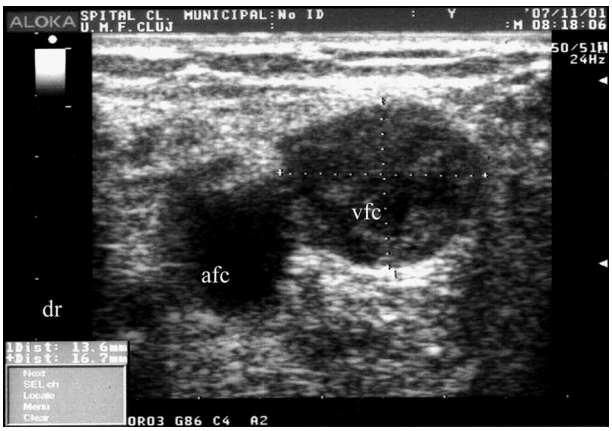


Fig 1. Short-axis view of the right common femoral vessels. Heterogenous hypoechoic intraluminal material dilating the common femoral vein. vfc: common femoral vein; afc: common femoral artery. dr: right lower extremity

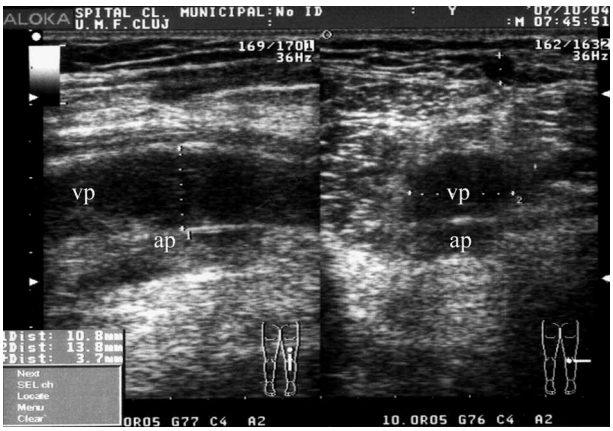


Fig 2. Longitudinal and transverse images of the right popliteal vessels. Dilated popliteal vein with heterogenous intraluminal deposition of thrombotic material. vp: popliteal vein; ap: popliteal artery.

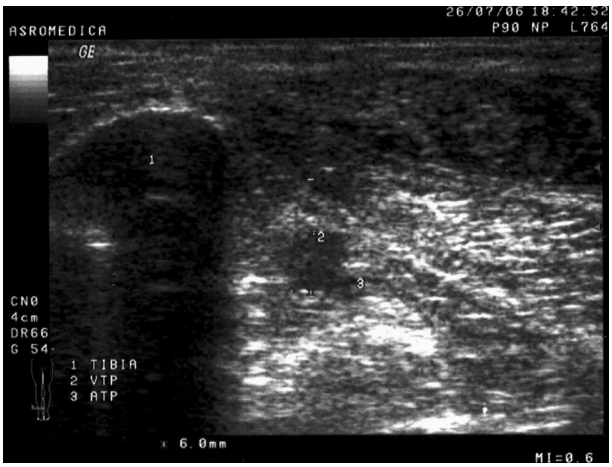


Fig 3. Short-axis view of the right calf. Increased cross-sectional diameter of a posterior tibial vein. VTP: posterior tibial vein; ATP: posterior tibial artery.

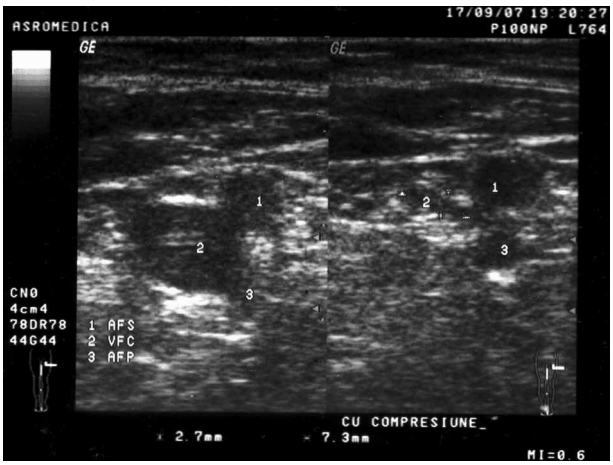


Fig 4. Transverse view of the left femoral vessels. Left side: without compression. Right side: with compression. Common femoral vein with nonocclusive thrombus. 1 (AFS): superficial femoral artery; 2 (VFC): common femoral vein; 3 (AFP): deep femoral artery.

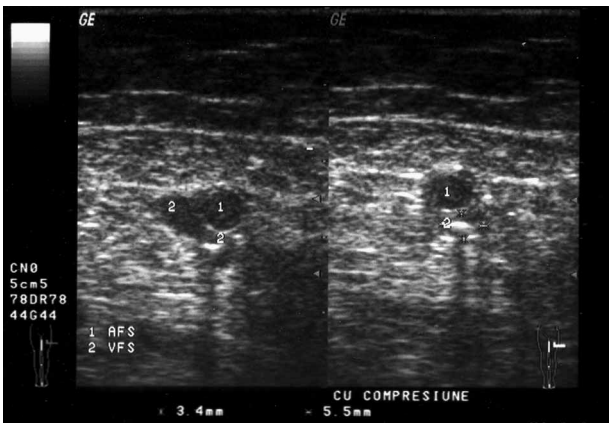


Fig 5. Short-axis view of the left superficial femoral vessels. Left side: without compression. Right side: with compression. Decreased cross-sectional diameter of the superficial femoral vein, nonocclusive intraluminal material. 1 (AFS): superficial femoral artery; 2 (VFS): superficial femoral vein.



Fig 6. Transverse view of the right popliteal vessels. Intraluminal echogenic material without shadowing. A POPL: popliteal artery; V POPL: popliteal artery.

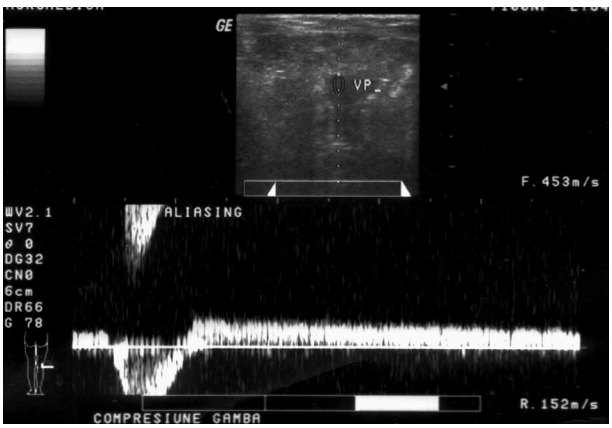


Fig 7. Short-axis view of the right popliteal vein. Distal compression maneuver detecting a long venous reflux. VP: popliteal vein.

Characteristics of patients included in our study are presented in Table I.

Some patient characteristics had a p-value less than 0.1: personal history of DVT ($p<0.001$), left side of lesions - acute thrombus and chronic thrombotic scarring ($p=0.08$), iliac vein involvement ($p=0.09$), femoral location of thrombi ($p=0.1$) and male gender ($p=0.1$). We performed unconditional logistic regression with these five factors (Table II).

As can be seen in Table II, only two features showed a statistically significant correlation with the presence of chronic thrombotic scarring in patients with acute DVT: personal history of DVT ($p<0.0001$) and thrombosis located in the left lower extremity ($p=0.0244$).

Discussion

The mean age of our patients was approximately 65 years. It is known that incidence and prevalence of DVT increases with increasing age [14]. For example, in people over 80 years, the incidence of DVT can reach a value of 10‰year [15,16]. Caprini [17] has developed a useful tool in determining thrombotic risk score (Total Risk Factor Score) according to which DVT prophylaxis should be performed. According to age, each patient receives one, two or three points, as follows: one point (age between 41 and 60 years), two points (age between 60 and 74 years) and three points (age over 75 years). For example, the three points characterize the DVT high risk so that patients require prophylaxis with heparin [17].

Of the 88 patients included in the study, 47 were men. The male-to-female ratio in our sample was 1.14. Bauersachs et al [18] examined 1388 outpatients (658 men and 730 women) with confirmed DVT. They found that prevalence of DVT was higher in men and proximal DVT was more frequent in men than in women (59.6% vs 44.5%, $p<0.001$). Andreou et al [19] examined 1838 outpatients and found that the prevalence of DVT was higher in men compared to women (14.4% vs 9.4%, $p=0.001$).

The most common RF were varicosis and obesity (found in more than one third of patients), personal history of DVT (27.2%) and active cancer (15.9%). Caprini [17] gave one point for varicose vein and obesity, two points for cancer and three points for DVT personal history. In patients with cancer, thromboembolic disease is the second leading cause of death [20].

Table I. Patient characteristics

Parameters	Group A N=28	Group B N=60	OR	95% CI*	p
Men	19	28	2.41	0.86-6.91	0.1
Age (mean ± standard deviation, median, range)	65.5±13.3 65 (35-86)	64.6±14.3 69 (23-84)	–	–	0.78
41-59 years	7	15	–	–	–
60-74 years	9	25	0.77	0.2-2.93	0.89
≥75 years	9	13	1.48	0.36-6.13	0.75
Major general surgery	1	1	2.19	0.0-83.72	0.54
Personal history of DVT	17	7	11.7	3.49-41.12	**<0.001**
Malignancy	6	8	1.77	0.47-6.56	0.25
Respiratory diseases	5	6	1.96	0.46-8.28	0.24
Stroke	0	3	0.7	0.03-8.21	0.62
Chemotherapy	3	0	0.7	0.03-8.21	0.62
Arthroscopic knee surgery	0	1	2.19	0.0-83.72	0.54
Varicose veins	14	24	1.5	0.55-4.08	0.51
Obesity	13	18	2.02	0.73-5.66	0.21
Immobilization > three days	1	7	0.28	0.01-2.49	0.21
Tibioperoneal	18	31	1.68	0.61-4.71	0.38
Muscular (soleo-gemelar)	18	29	1.92	0.7-5.38	0.24
Popliteal	14	25	1.4	0.52-3.8	0.61
Femoral	16	22	2.33	0.84-6.37	0.12
Iliac	6	4	3.82	0.84-18.2	0.09
Left-sided DVT	18	25	2.52	0.91-7.09	0.08
Right-sided DVT	13	20	1.73	0.63-4.79	0.34

* 95% confidence interval

Table II. Unconditional logistic regression with five factors

Factors	OR	95% CI	p
Men	2.1081	0.6778-6.5571	0.1977
Personal history of DVT	20.3202	4.8501-85.1343	**<0.0001**
Femoral	0.9677	0.2759-3.3949	0.9591
Iliac	2.0399	0.3310-12.5696	0.4423
Left side DVT	5.0128	1.2313-20.4076	**0.0244**

In our study, more than half of the thrombi were located in the calf. A total of 106 of the 239 patients examined by Pennell et al [21], representing 44.4%, had calf thrombosis. Calf thrombosis is important because it is known that calf vein thrombosis involves the proximal veins in 25% of patients [1].

The left side-to-right side ratio was 1.30. Virchow (1851), cited by Ludwig et al [22], found that DVT occurs five times more frequently in the left leg versus right leg.

Thrombi were located bilaterally in 13.7% of our patients. Bilateral thrombosis was encountered in 19.7% of symptomatic cases of Pennell et al [21]. Clinically silent contralateral thrombosis was diagnosed in 34% of their patients.

PTS frequency in our patients was 31.8%. Labropoulos et al [23] followed 153 patients for 5 years after acute episode of DVT. Recurrence rate was 26.1% in these patients. Brandjes et al [7] found a frequency of 20%. Percentage of Hennerici et al [5] is at least double - 40-50%. A total of 50 of the 490 patients included in the PROLONG Study had recurrent DVT (12.2%) [24].

In our study PTS correlated with personal history of thromboembolism and previous thrombosis of the left extremity. According to The Prospective Investigation of Pulmonary Embolism Diagnosis II (PIOPED II), the recurrence probability is twofold for those with a personal history of thromboembolism [9]. Labropoulos et al [23] found that factors associated with DVT recurrence were

unprovoked DVT (relative risk 2.9) and age more than 65 years (relative risk 1.5).

Limitations

There were no patients with the following RF: pregnancy, oral contraceptives, hormone replacement therapy, polycythemia vera, total hip or knee replacement, arthroscopic procedures, laparoscopic surgery, spinal cord injuries and major trauma.

We could not evaluate thrombophilia.

Conclusion

In our study, PTS correlated with personal history of thromboembolism and previous left lower leg thrombosis.

Competing interest

No conflict of interest.

References

1. Ansell JE. Venous thrombosis. In: Creager MA, Dzau VJ, Loscalzo J (eds). Vascular medicine. A companion to Braunwald's heart disease. Philadelphia, Saunders Elsevier 2006: 743-764.
2. Kucher N, Goldhaber SZ. Pulmonary embolism. In: Creager MA, Dzau VJ, Loscalzo J (eds). Vascular medicine. A companion to Braunwald's heart disease. Philadelphia, Saunders Elsevier 2006:765-776.
3. Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. Circulation 2003; 107(23 Suppl 1): I9 -I16.
4. Nasim A, London NJM. Venous thromboembolic disease. In: Donnelly R, London JMN (eds). ABC of arterial and venous disease, 2nd ed, Chicester, West Sussex, UK, Wiley-Blackwell 2009: 67-71.
5. Hennerici MG, Neuerburg-Heusler D, Daffertshofer M, Karasch T, Meairs S. Vascular diagnosis with ultrasound. Clinical reference with case studies. Volume 1: Cerebral and peripheral vessels. 2nd revised ed, Stuttgart-New York, Thieme 2006: 211-256.
6. Bundens WP, Bergan JJ. Definitive diagnosis and documentation of chronic venous dysfunction. In: Zwiebel WJ (ed). Introduction to vascular ultrasonography. 4th edition, Philadelphia, W.B.Saunders Company 2000: 347-368.
7. Brandjes DP, Büller HR, Heijboer H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. Lancet 1997; 349: 759-762.
8. Lyman GH, Khorana AA, Falanga A, et al. American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. J Clin Oncol 2007; 25: 5490-5505.
9. Goodman LR, Stein PD, Matta F, et al. CT venography and compression sonography are diagnostically equivalent: data from PIOPED II. AJR Am J Roentgenol 2007; 189: 1071-1076.
10. Scarvelis D, Wells PS. Diagnosis and treatment of deep-vein thrombosis. CMAJ 2006; 175: 1087-1092.
11. Segal JB, Eng J, Tamariz LJ, Bass EB. Review of the evidence on diagnosis of deep venous thrombosis and pulmonary embolism. Ann Fam Med 2007; 5: 63-73.
12. ICSI (Institute for Clinical Systems Improvement) Health Care Guideline: Venous thromboembolism diagnosis and treatment. 10th Edition, February 2010 http://www.icsi.org/venous_thromboembolism/venous_thromboembolism_4.html (website accessed on March 21, 2010).
13. Zwiebel WJ. Venous thrombosis. In: Zwiebel WJ (ed). Introduction to vascular ultrasonography. 4th edition, Philadelphia, W.B.Saunders Company 2000: 329-345.
14. Weill-Engerer S, Meaume S, Lahlou A, et al. Risk factors for deep vein thrombosis in inpatients aged 65 and older: a case-control multicenter study, J Am Geriatr Soc 2004; 52: 1299-1304.
15. Rosendaal FR, VAN Hylckama Vlieg A, Doggen CJ. Venous thrombosis in the elderly. J Thromb Haemost 2007; 5 (Suppl.1): 310-317.
16. Snow V, Qaseem A, Barry P, et al. Management of venous thromboembolism: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann Fam Med 2007; 5: 74-80.
17. http://www.crmhealthcare.net/docs/67450a_Caprini-RiskAssesemntTool.pdf (website accessed on March 22, 2010)
18. Bauersachs RM, Riess H, Hach-Wunderle V, et al. Impact of gender on the clinical presentation and diagnosis of deep-vein thrombosis. Thromb Haemost 2010; 103: 710-717.
19. Andreou ER, Koru-Sengul T, Linkins L, Bates SM, Ginsberg JS, Kearon C. Differences in clinical presentation of deep vein thrombosis in men and women. J Thromb Haemost 2008; 6: 1713-1719.
20. Khorana AA. The NCCN Clinical Practice Guidelines on Venous Thromboembolic Disease: strategies for improving VTE prophylaxis in hospitalized cancer patients. Oncologist 2007; 12: 1361-1370.
21. Pennell RC, Mantese VA, Westfall SG. Duplex scan for deep vein thrombosis – defining who needs an examination of the contralateral asymptomatic leg. J Vasc Surg 2008; 48: 413-416.
22. Ludwig B, Han T, Amundson D. Postthrombotic syndrome complicating a case of May-Thurner syndrome despite endovascular therapy: case report and review. Chest 2006; 129: 1382-1386.
23. Labropoulos N, Jen J, Jen H, Gasparis AP, Tassiopoulos AK. Recurrent deep vein thrombosis: long-term incidence and natural history. Ann Surg 2010 Mar 10. [Epub ahead of print].
24. Cosmi B, Legnani C, Iorio A, et al; PROLONG Investigators (on behalf of FCSA Italian Federation of Anticoagulation Clinics). Residual venous obstruction, alone and in combination with D-dimer, as a risk factor for recurrence after anticoagulation withdrawal following a first idiopathic deep vein thrombosis in the prolong study. Eur J Vasc Endovasc Surg 2010; 39: 356-365.