# Minor Injuries as a Risk Factor for Venous Thrombosis

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**Background:** Injuries increase the risk of venous thrombosis. So far, most research has focused on major injuries that are accompanied by other risk factors for venous thrombosis, such as plaster casts and surgery. We studied the association of venous thrombosis with common minor injuries, such as minor sural muscle ruptures and ankle sprains.

**Methods:** We performed a large, population-based, case-control study (the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis [MEGA] study), including consecutive patients with a first deep venous thrombosis of the leg or pulmonary embolism and control subjects. Participants with malignant neoplasms, those who underwent surgery, and those who had a plaster cast or extended bed rest were excluded.

**Results:** Of 2471 patients, 289 (11.7%), and of 3534 controls, 154 (4.4%) had a minor injury in the 3 months preceding the venous thrombosis (patients) or completion of the questionnaire (controls). Venous thrombosis was associated with previous minor injury (odds ratio adjusted for sex and age, 3.1; 95% confidence interval, 2.5-3.8). The association was strongest for injuries that occurred in the 4 weeks before thrombosis and was not apparent before 10 weeks. Thrombosis was more strongly associated with minor injuries located in the leg (odds ratio adjusted for sex and age, 5.1; 95% confidence interval, 3.9-6.7), while those located in other body parts were not associated. A 50-fold increased risk was found in factor V Leiden carriers with a leg injury compared with noncarriers without injury (odds ratio, 49.7; 95% confidence interval, 6.8-362.7).

**Conclusions:** Minor injuries in the leg are associated with greater risk of venous thrombosis. Because minor injuries are common, they could be major contributors to the occurrence of venous thrombosis.

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VENOUS THROMBOSIS IS A multicausal disease affecting 1 to 3 per 1000 individuals each year.[1,2] Known risk factors are, among others, surgery, immobility, and several prothrombotic genetic variants.[3] So far, studies[4-11] have focused on major injuries in hospitalized or deceased individuals; they were found to be major risk factors for venous thrombosis. However, apart from the injury itself, other risk factors for venous thrombosis will be present because of the major injury, such as surgery, a plaster cast, hospitalization, and extended bed rest. The risk of so-called minor injuries that do not lead to these additional factors is unknown. We set up a large, population-based, case-control study into the cause of venous thrombosis, the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) study. The present study had 4 main objectives: (1) to estimate the relative risk of venous thrombosis after a minor injury; (2) to investigate characteristics of minor injuries that contribute most to this risk, such as location and type of injury; (3) to estimate the relative risk of venous thrombosis of common injuries; and (4) to identify high-risk patients by assessing the joint effect of minor injuries with well-known genetic predispositions.

*For editorial comment see page 14*

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## METHODS

### PARTICIPANTS

From March 1, 1999, until August 31, 2004, all consecutive patients with a first episode of venous thrombosis were recruited from 6 anticoagulation clinics in the Netherlands. These clinics monitor the anticoagulant treatment of all patients within a well-defined geographical area.

All patients had a first episode of deep venous thrombosis (DVT) in the leg or a

**Table 1. Characteristics of the Study Population[a]**

| Characteristic | Patients (n=2471) | Control Subjects (n=3534) |
|---|---|---|
| Women, % | 53.2 | 53.3 |
| Age, y | 47.8 (24.9-67.6) | 46.2 (24.8-66.5) |
| BMI | 27.0 (20.3-35.4) | 25.4 (19.8-33.0) |
| Type of venous thrombosis[b] | | |
| PE | 766 (31.0) | NA |
| DVT | 1454 (58.8) | NA |
| DVT (leg) plus PE | 251 (10.2) | NA |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DVT, deep venous thrombosis; NA, data not applicable; PE, pulmonary embolism.

[a] Data are given as median (5th-95th percentile) unless otherwise indicated.

[b] Data are given as number (percentage) of patients.

pulmonary embolism (PE) between the ages of 18 and 70 years. Of the 6331 eligible patients, 276 died before they were able to fill out a questionnaire, while 82 had a short life expectancy and, therefore, did not participate in this study. Of the remaining eligible individuals, 5051 (84.6%) participated.

Information regarding the diagnostic procedure was obtained via hospital records and family physicians for 4059 patients. A DVT was considered definite when (Doppler) ultrasonography showed the presence of a thrombus in the deep veins. A PE was considered definite when confirmed with a high-probability ventilation-perfusion scan, positive spiral computed tomographic findings, or positive angiographic findings. A PE was considered probable when the diagnosis was based on a low- or intermediate-probability ventilation-perfusion scan, inconclusive spiral computed tomographic findings, or inconclusive angiographic findings. For some patients, no information regarding the diagnostic procedure was available, while other patients were registered at the anticoagulation clinic with a different or additional diagnosis than the one objectively confirmed. In those patients, the diagnosis by which the patient was registered at the anticoagulation clinic was added. For these patients, we considered a registered PE as probable and a registered DVT as definite. Only 4958 patients were included in whom the diagnosis was considered definite or probable.

Control subjects were included from 2 sources: (1) by inviting partners of patients (81.6% of the partners participated) and (2) by using a random-digit–dialing method (68.8% participated).[12] All participants gave written informed consent. This study was approved by the Medical Ethics Committee of the Leiden University Medical Center.

## DATA COLLECTION

In a standardized questionnaire participants reported injuries, surgical procedures, plaster casts, and immobilizations covering the period 1 year before the index date along with sport activities, standing height and weight, and family history of venous thrombosis. Body mass index was calculated as weight in kilograms divided by height in meters squared. The index date was defined as the date of diagnosis of the thrombotic event for the patients and the date of completing the questionnaire for the controls. The questionnaire was sent to all participants within a few weeks after registration at the anticoagulation clinic or after we contacted the individuals in the random-digit–dialing control group. During the first few months of the study, a pilot questionnaire was used that did not contain questions regarding injuries. These 156 patients and 41 controls were excluded.

Participants were asked to report the most recent injury before the index date in a separate specific question related to minor injuries. The questionnaire listed 8 common injuries and included an open text field for other injuries. The injuries were categorized irrespective of patient or control status. Seventeen patients who reported an injury after their venous thrombotic event were excluded. Only injuries that occurred in the 3 months before the index date were included in the present analysis. Subjects who underwent surgery or had a plaster cast, a hospitalization, or extended bed rest at home for at least 4 days in the year before the index date were excluded (1631 patients and 1004 controls), as were individuals who had ever been diagnosed as having malignant neoplasms before the index date (580 patients and 233 controls).

An additional 1396 partner controls were excluded because their corresponding patient was excluded for one of the reasons previously mentioned.

## DNA COLLECTION AND LABORATORY ANALYSES

Patients and their partners who were included between March 1, 1999, and May 31, 2002, and the random control group were invited to the anticoagulation clinic for a blood draw. Patients and their partners recruited from June 1, 2002, onward and participants who were unable or unwilling to come to the anticoagulation clinic were sent buccal swabs to collect DNA. Factor V Leiden and the prothrombin 20210A mutation were measured simultaneously.[13]

## STATISTICAL ANALYSIS

Odds ratios (ORs) were calculated as estimates of the relative risk of thrombosis with 95% confidence intervals (CIs). Odds ratios were adjusted for sex and age ($OR_{adj}$). Partners were matched to their patients to adjust for lifestyle factors, resulting in 1260 eligible couples in a matched analysis, while all 2538 patients were contrasted to the random-digit–dialing controls (2331 subjects) in an unmatched analysis. For calculation of the overall risk, we weighted the OR of the matched analysis with the OR obtained by the unmatched analysis. This contained an adjustment for patients included in matched and unmatched analysis (the authors may be contacted for additional information). When analyzing the risk in men and women separately, only random control subjects were used; as in most couples, partners were of the opposite sex.

The percentage of injuries per week was calculated by dividing the number of individuals with an injury during a particular week by the total number of individuals who did not have an injury before that date. We calculated the proportion of calf vein thrombosis events and CIs using the exact method. To assess the joint effect of injuries and the factor V Leiden and prothrombin 20210A mutations, ORs were calculated in the presence of only 1 risk factor and in the presence of both risk factors, all relative to those individuals with neither risk factor. We also performed a case-only analysis, which results in a synergy index (SI). An SI of 1 or more indicates synergy on a multiplicative scale. All analyses were performed using SAS statistical software, version 9.1 (SAS Institute Inc, Cary, North Carolina).

# RESULTS

Overall, 2471 patients and 3534 controls were included in the present analysis. Their characteristics are shown

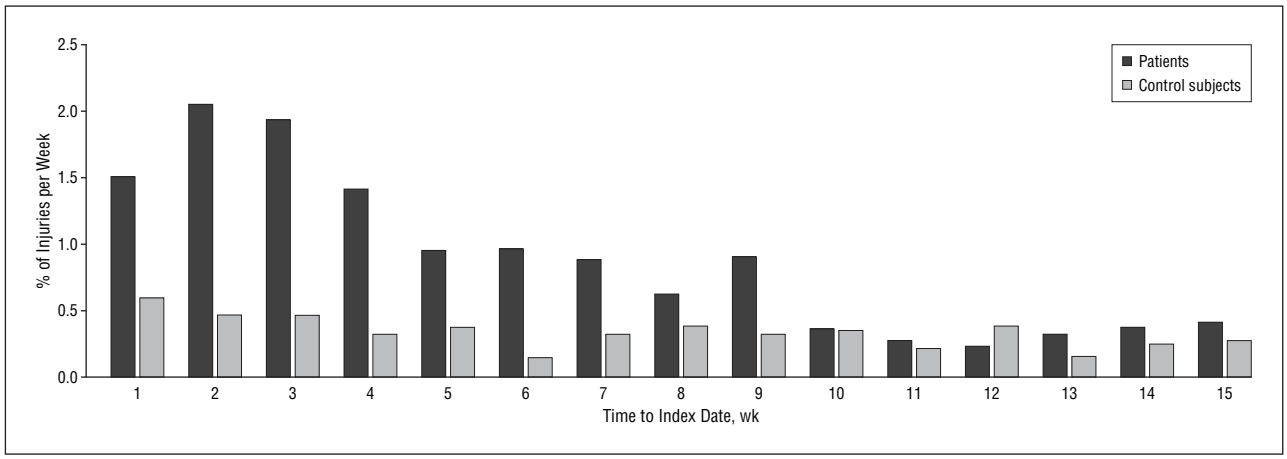


**Figure.** Percentage of injuries per week before the index date, which was the diagnosis of venous thrombosis (in patients) or completion of the questionnaire (in control subjects). The time window of the analysis concerned the first 13 weeks.

in **Table 1**. Control subjects with injuries were slightly more often men (52.6% vs 46.6%) and younger (mean age, 44.3 vs 46.9 years) compared with those without injuries (data now shown).

Of the patients, 289 (11.7%) had a minor injury in the 3 months before the index date, as did 154 controls (4.4%). Injury was associated with venous thrombosis (OR, 3.0; 95% CI, 2.4-3.6). Adjustment for sex and age did not change this estimate ($OR_{adj}$, 3.1; 95% CI, 2.5-3.8) nor did further adjustment for sport activities and body mass index ($OR_{adj}$, 3.5; 95% CI, 2.8-4.3). Injury in 67 patients and 57 controls who did not mention a specific date of the injury was not associated with venous thrombosis ($OR_{adj}$, 1.2; 95% CI, 1.1-1.3). These individuals were excluded from all analyses. Random control subjects had injuries slightly more often (4.8%) than partner controls (3.6%) in the 3 months before the index date, resulting in slightly different estimates: the $OR_{adj}$ of random controls was 2.8 (95% CI, 2.3-3.6) and that of partner controls was 4.2 (95% CI, 2.9-6.0).

Thrombosis was more strongly associated with injuries that occurred during the previous 4 weeks ($OR_{adj}$, 4.0; 95% CI, 2.8-5.9) than with less recent injuries (**Figure**). Among patients, most injuries occurred in the 2 to 3 weeks before the venous thrombosis diagnosis, while fewer events occurred in the week directly before the venous thrombosis.

In the 3-month time window, ORs for minor injuries were similar in men ($OR_{adj}$, 3.0; 95% CI, 2.1-4.1) and women ($OR_{adj}$, 3.0; 95% CI, 2.2-4.2), as were ORs for the young vs old (young [aged 18-39 years]: $OR_{adj}$, 3.3 [95% CI, 2.3-4.6]; middle aged [40-59 years]: $OR_{adj}$, 3.1 [95% CI, 2.3-4.2]; and old [aged ≥60 years]: $OR_{adj}$, 3.3 [95% CI, 1.5-7.4]).

## LOCATION OF INJURY

Of the 289 patients with a minor injury, 237 (82.0%) had their injury located in the leg, compared with 78 of 154 injuries (50.6%) among controls. Therefore, thrombosis was more strongly associated with injury in the leg than with injury located in other body parts (overall $OR_{adj}$, 1.1; 95% CI, 0.8-1.6) (**Table 2**).

**Table 2. Location of Injury and Risk of Venous Thrombosis**

| Location | Patients (n=2471)[a] | Control Subjects (n=3534)[a] | Odds Ratio (95% Confidence Interval)[b] |
|---|---|---|---|
| None (no injury) | 2182 | 3380 | 1 [Reference] |
| Leg | 237 | 78 | 5.1 (3.9-6.7) |
| Arm | 23 | 43 | 0.8 (0.5-1.4) |
| Trunk | 14 | 24 | 0.9 (0.5-1.9) |
| Head | 1 | 4 | 0.3 (0-2.4) |
| Unknown | 14 | 5 | 3.0 (1.1-8.3) |

[a] Data are given as number of individuals in each group.
[b] Adjusted for sex and age.

Injuries in the leg were mainly associated with greater relative risk of an isolated DVT ($OR_{adj}$, 6.3; 95% CI, 4.7-8.5). The relative risk of an isolated PE ($OR_{adj}$, 2.4; 95% CI, 1.6-3.7) or a combination of PE and DVT ($OR_{adj}$, 5.3; 95% CI, 3.2-8.7) was also greater. For 1101 patients with a DVT, information was available regarding the location of the thrombus. Patients with a leg injury more often had a DVT in isolated calf veins (26.3%; 95% CI, 18.9%-33.6%) compared with patients without an injury (14.5%; 95% CI, 12.3%-16.7%).

## TYPES OF INJURY

(Partial) ruptures of muscles or ligaments in the leg were more strongly associated with a venous thrombosis than were other injuries, such as sprains and contusions. Multiple injuries occurring simultaneously were strongly associated with venous thrombosis (**Table 3**).

Specific injuries most strongly associated with thrombosis were ruptures of the sural muscle ("tennis legs") and knee ligament ruptures, while knee and ankle sprains were associated to a lesser extent with venous thrombosis (**Table 4**).

## PROTHROMBOTIC FACTORS

In individuals who indicated having a first-degree family member with a history of venous thrombosis, leg injury was associated with an estimated 12-fold relative

**Table 3. Type of Injury in the Leg and Risk of Venous Thrombosis**

| Type of Injury | Patients (n=2419)[a] | Control Subjects (n=3458)[a] | Odds Ratio (95% Confidence Interval)[b] |
|---|---|---|---|
| No injury | 2182 | 3380 | 1 [Reference] |
| Muscle or ligament rupture | 70 | 11 | 10.9 (5.6-21.3) |
| Contusion | 6 | 5 | 2.0 (0.5-7.6) |
| Sprain | 77 | 40 | 3.1 (2.1-4.6) |
| Multiple types of injury | 24 | 4 | 9.9 (3.3-29.6) |
| Other | 33 | 8 | 6.9 (3.1-15.0) |
| Unknown | 27 | 10 | 4.6 (2.2-9.8) |

[a] Data are given as number of individuals in each group.
[b] Adjusted for sex and age.

**Table 4. Specific Injuries in the Leg and Their Risk of Venous Thrombosis**

| Specific Injury | Patients[a] | Control Subjects[a] | Odds Ratio (95% Confidence Interval)[b] |
|---|---|---|---|
| No injury | 2182 | 3380 | 1 [Reference] |
| Rupture of the sural muscle ("tennis legs") | 56 | 5 | 22.5 (8.3-61.5) |
| Rupture of the knee ligaments | 24 | 6 | 6.3 (2.6-15.0) |
| Ankle sprain | 39 | 24 | 2.6 (1.6-4.1) |
| Knee sprain or meniscus problems | 47 | 16 | 5.1 (2.9-8.9) |

[a] Data are given as number of individuals in each group.
[b] Adjusted for sex and age.

**Table 5. Joint Effect of Prothrombotic Mutations and Injuries in the Leg**

| Prothrombotic Mutation | Injuries | Patients (n=2243)[a] | Control Subjects (n=2639)[a] | Odds Ratio (95% Confidence Interval)[b] |
|---|---|---|---|---|
| Factor V Leiden | | | | |
| Absent | Absent | 1623 | 2388 | 1 [Reference] |
| Present | Absent | 351 | 135 | 5.0 (4.0-6.2) |
| Absent | Present | 181 | 59 | 6.8 (4.9-9.4) |
| Present | Present | 39 | 1 | 49.7 (6.8-362.7) |
| Factor II 20210A mutation | | | | |
| Absent | Absent | 1874 | 2477 | 1 [Reference] |
| Present | Absent | 100 | 46 | 3.4 (2.3-5.0) |
| Absent | Present | 206 | 55 | 7.0 (5.1-9.6) |
| Present | Present | 14 | 2 | 8.6 (1.9-37.9) |

[a] Data are given as number of individuals in each group.
[b] Adjusted for sex and age.

risk of venous thrombosis ($OR_{adj}$, 12.0; 95% CI, 5.9-24.7) compared with no injury in individuals without a family history. This finding suggests a joint effect with genetic factors. The estimated relative risk in carriers of the factor V Leiden mutation with an injury compared with noncarriers without an injury was almost 50 (**Table 5**). Because the number of controls with an injury and the factor V Leiden mutation was small, an SI calculation in only patients was performed. This calculation (SI=[1623×39]/[351×181]=1.0) suggested a joint effect at a multiplicative level and a 30-fold (1.0×5.0×6.8=34) relative risk for those having the factor V Leiden mutation and a leg injury compared with those having neither the factor V Leiden mutation nor injuries. The prothrombin 20210A mutation was associated with a 3-fold estimated relative risk of venous thrombosis among those without an injury. When both risk factors were present, the estimated relative risk of venous thrombosis was 9-fold compared with individuals without injury and the prothrombin 20210A mutation. The SI calculation (SI=[1874×14]/[206× 100]=1.3) suggested interaction at a multiplicative level and a 30-fold (1.3×3.4×7.0=30) relative risk for the joint effect of the prothrombin 20210A mutation and leg injuries.

## COMMENT

Minor injuries that do not require surgery, a plaster cast, or extended bed rest were associated with a 3-fold greater relative risk of venous thrombosis. The association appeared local because injuries in the leg were associated strongly with thrombosis, while injuries in other locations were not associated with thrombosis. The association was strongest for injuries that occurred in the month before the venous thrombosis, suggesting a transient effect. The association of thrombosis with leg injuries was strong in individuals with a genetic predisposition.

Most studies have focused on major or even fatal injuries. Because these studies were performed in hospitals, individuals who had an injury were also hospitalized and immobilized. Therefore, it is difficult to make a distinction between the effect of hospitalization, surgery, a plaster cast, and extended bed rest and the effect of injury. In studies[7-9,14] that focused on major injuries, an asymptomatic venous thrombosis was detected in 0.4% to 12% of the trauma patients, despite prescribed prophylaxis. One study[15] found a 3-fold increased risk of venous thrombosis after minor events. However, minor events included, among others, travel, minor surgery, and

minor trauma, and no information regarding minor trauma alone was available. Therefore, the risk of minor injuries could not be abstracted.

We found that the association of venous thrombosis with minor injuries was transient and that the excess risk disappeared after 10 weeks. Surprisingly, more injuries were found in the 2 to 3 weeks before the venous thrombosis compared with the week directly before the venous thrombosis. Although the differences were small and chance variation may have occurred, this difference may be true. It may take time before a clot becomes clinically apparent. However, this seems less probable because venous thrombosis rates after air travel were highest in the first week after air travel.[16] More likely, because of the symptoms of the injury itself, the patient and physician may not recognize the venous thrombosis at first because the clinical characteristics are similar.

Injuries were strongly associated with venous thrombosis in individuals with genetic predisposition or a family history of venous thrombosis. We found a 50-fold increased relative risk estimate in individuals with a factor V Leiden mutation and an injury. Because the risk associated with venous thrombosis was highest in the first month after the injury and decreased sharply thereafter, we believe that many cases of venous thrombosis could be prevented when high-risk individuals with injuries would receive short-term prophylactic treatment. However, data are scarce and future research is needed to show whether this would be safe.

Several reasons why injuries are associated with the risk of venous thrombosis are conceivable. In 1856, Virchow[17] described 3 main risk factors for thrombosis: hypercoagulability, stasis of the blood, and damage of the vessel wall. First, several studies[18,19] have shown an increased prothrombotic state in severely injured patients. However, this increased prothrombotic state was not predictive of venous thrombosis in severely injured patients.[19] Because injuries not located in the leg were not associated with a higher risk of venous thrombosis in our study, we do not believe that a systemic reaction to minor injuries explains the thrombotic risk. Second, immobilization leading to stasis of the blood could play an important role. To rule out this effect, we excluded individuals with extended bed rest or immobilization due to plaster casts. However, even minor injuries could have led to reduced mobility, not necessarily bed rest, which could have led to thrombosis. Obstruction of the vein by edema may have caused stasis as well. Third, damage of the vessel wall because of an injury may lead to local increased risk of venous thrombosis.

Information on minor injuries was obtained after the thrombotic event. Patients could link their injuries to the thrombosis and, therefore, report the injury in the questionnaire, whereas controls do not have a specific event through which they can remember their injuries and, therefore, may not remember their injury (recall bias). However, the questionnaire for controls covered the period before filling it out. Because risks were only increased up to 10 weeks, it seems likely that controls will have remembered their minor events during this period. A second reason why recall bias seems doubtful is that the risk of PE was also markedly increased and patients probably do not link their leg injury to PE. Referral bias could have occurred if physicians would be more likely to diagnose or refer an injured patient for venous thrombosis examination. This would lead to an overestimation of the risk of venous thrombosis after injury. One study,[20] also from the Netherlands, could not find a higher risk of being referred for venous thrombosis among women using oral contraceptives. However, we do not know whether this is also true for minor injuries.

Our study showed that 4.4% of the controls had a minor injury in the 3 months before the index date. Because minor injuries are common, they can be responsible for many cases of venous thrombosis, as can be shown by the population-attributable fraction. Of the patients, 289 of 2471 (11.7%) had a minor injury. The risk of venous thrombosis was 3-fold increased, resulting in a population-attributable fraction of 7.9% ($[11.7 \times \{3.1-1\}]/3.1=7.9$). Because other injuries were not associated with venous thrombosis risk, this population-attributable fraction was entirely due to injuries in the leg (7.7%). This suggests that minor injuries in the leg may be involved in 8% of the venous thrombotic events. The risk of venous thrombosis was estimated after minor injuries that did not require a plaster cast, hospitalization, or extended bed rest. Because minor injuries are common, they can be major contributors to the occurrence of venous thrombosis. Many individuals with minor injuries will have contacted the general practitioner first. Therefore, there may be an important task for general practitioners to identify subjects who are at a high risk of developing venous thrombosis and subsequently to provide prophylactic measures.

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## REFERENCES

1. Oger E; EPI-GETBP Study Group (Groupe d'Etude de la Thrombose de Bretagne Occidentale). Incidence of venous thromboembolism: a community-based study in Western France. *Thromb Haemost*. 2000;83(5):657-660.
2. Nordström M, Lindblad B, Bergqvist D, Kjellström T. A prospective study of the incidence of deep-vein thrombosis within a defined urban population. *J Intern Med*. 1992;232(2):155-160.
3. Rosendaal FR. Venous thrombosis: a multicausal disease. *Lancet*. 1999;353(9159): 1167-1173.
4. McCartney JS. Pulmonary embolism following trauma. *Surg Gynecol Obstet*. 1935; 61:369-379.
5. Fitts WT Jr, Lehr HB, Bitner RL, Spelman JW. An analysis of 950 fatal injuries. *Surgery*. 1964;56:663-668.
6. Coon WW. Risk factors in pulmonary embolism. *Surg Gynecol Obstet*. 1976;143 (3):385-390.
7. Geerts WH, Code KI, Jay RM, Chen E, Szalai JP. A prospective study of venous thromboembolism after major trauma. *N Engl J Med*. 1994;331(24):1601-1606.
8. Knudson MM, Ikossi DG. Venous thromboembolism after trauma. *Curr Opin Crit Care*. 2004;10(6):539-548.
9. Knudson MM, Ikossi DG, Khaw L, Morabito D, Speetzen LS. Thromboembolism after trauma: an analysis of 1602 episodes from the American College of Surgeons National Trauma Data Bank. *Ann Surg*. 2004;240(3):490-496.
10. Gearhart MM, Luchette FA, Proctor MC, et al. The risk assessment profile score identifies trauma patients at risk for deep vein thrombosis. *Surgery*. 2000;128 (4):631-640.
11. Schultz DJ, Brasel KJ, Washington L, et al. Incidence of asymptomatic pulmonary embolism in moderately to severely injured trauma patients. *J Trauma*. 2004; 56(4):727-731.
12. van Stralen KJ, Le Cessie S, Rosendaal FR, Doggen CJM. Regular sports activities decrease the risk of venous thrombosis. *J Thromb Haemost*. 2007;5(11): 2186-2192.
13. Gomez E, van der Poel SC, Jansen JH, van der Reijden BA, Lowenberg B. Rapid simultaneous screening of factor V Leiden and G20210A prothrombin variant by multiplex polymerase chain reaction on whole blood. *Blood*. 1998;91(6): 2208-2209.
14. Lassen MR, Borris LC, Nakov RL. Use of the low-molecular-weight heparin reviparin to prevent deep-vein thrombosis after leg injury requiring immobilization. *N Engl J Med*. 2002;347(10):726-730.
15. Eekhoff EM, Rosendaal FR, Vandenbroucke JP. Minor events and the risk of deep venous thrombosis. *Thromb Haemost*. 2000;83(3):408-411.
16. Cannegieter SC, Doggen CJ, van Houwelingen HC, Rosendaal FR. Travel-related venous thrombosis: results from a large population-based case control study (MEGA Study). *PLoS Med*. 2006;3(8):e307. doi:10.1371/journal.pmed.0030307.
17. Virchow R. *Phlogose und Thrombose im Gefässystem: Gesammelte Abhandlungen zur Wissenschaftlichen Medizin*. Frankfurt, Germany: Staatsdruckerei; 1856: 525.
18. Engelman DT, Gabram SG, Allen L, Ens GE, Jacobs LM. Hypercoagulability following multiple trauma. *World J Surg*. 1996;20(1):5-10.
19. Meissner MH, Zierler BK, Bergelin RO, Chandler WC, Manzo RA, Strandness DE Jr. Markers of plasma coagulation and fibrinolysis after acute deep venous thrombosis. *J Vasc Surg*. 2000;32(5):870-880.
20. Bloemenkamp KW, Rosendaal FR, Büller HR, Helmerhorst FM, Colly LP, Vandenbroucke JP. Risk of venous thrombosis with use of current low-dose oral contraceptives is not explained by diagnostic suspicion and referral bias. *Arch Intern Med*. 1999;159(1):65-70.