

Long-term survival after venous thromboembolism: a retrospective selected cohort study among young women

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ABSTRACT

Few data are available on long-term survival following venous thromboembolism. We performed a retrospective survival analysis covering the period January 1985 to December 2006 in 728 young women (median age 28.7 years; interquartile range 21.6-36.3 years) with a history of venous thromboembolism who visited our clinic between 1985 and 1998. Mortality information was obtained from the Austrian Central Death Register. Survival of our patients was compared to the general Austrian female population after adjustment for age and calendar period. Overall, 23 patients (3.2%) died, the cumulative relative survival was 1.03 (95% CI 0.99-1.04). Site of venous thromboembolism or triggering factors had no significant influence. Venous thromboembolism does not reduce long-term survival in young women considering our median follow up of 14

years. The risk of fatal bleeding and quality of life should be assessed versus that of fatal recurrent venous thromboembolism when deciding on long-term anticoagulation in young women.

Key words: venous thrombosis, pulmonary embolism, venous thromboembolism, survival, mortality.

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Introduction

Venous thromboembolism (VTE) is a severe clinical condition occurring either as deep venous thrombosis (DVT) and/or pulmonary embolism (PE). Venous thromboembolism is one of the most common cardiovascular diseases following myocardial infarction and stroke.¹

In developed countries, the incidence of venous thromboembolism is between 1 and 2 per 1,000 persons per year^{2,3} and pulmonary embolism still remains an important issue with a high mortality rate.⁴

About two-thirds of deep venous thrombosis episodes occur in conjunction with external factors, such as surgery, immobilization or trauma.⁵ For women there are further risk factors, namely pregnancy, puerperium and oral contraceptive use (OC). Also, there are demographic and conditional risk factors for initial venous thromboembolism: advanced age,^{6,7} obesity⁸ and cancer.

Data on survival after venous thromboembolism are scarce and vary considerably. Reports on short-term survival vary from 95% to 97% following deep venous thrombosis^{9,2} and from 77% to 94% following pulmonary embolism.^{2,7,10} Long-term survival rates for both deep venous thrombosis and pulmonary embolism range from 61% to 75%.^{2,7,8,11,12}

The aim of our study was to evaluate the long-term sur-

vival among women with venous thromboembolism at a relatively young age and to compare their survival to the general population.

Design and Methods

All women aged 13 to 45 with a history of venous thromboembolism who visited our outpatient clinic for routine coagulation screening between January 1985 and December 1998 and who had no malignancy at first presentation were included. The event had always been documented by objective methods, such as phlebography, plethysmography, duplex ultrasonography, perfusion ventilation lung scan or computed tomography. Short-term oral anticoagulation with vitamin K antagonists after the first deep venous thrombosis or pulmonary embolism was defined as up to six months; long-term anticoagulation was usually only recommended in patients with lupus anticoagulant, antithrombin deficiency or combined genetic defects.

A retrospective survival analysis of the above-mentioned patients for the period 1st January 1985 to 31st December 2006 was performed. The observation period started when the patient was first seen at our department (median 1.57 years following their first episode of VTE; IQR 0.41-8.7 years). In addition to patient file information, data on mortality was obtained from the Austrian Central Death Register, which is maintained by Statistics Austria. Causes of death were

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coded according to the International Classification of Diseases (ICD). Overall mortality of the general Austrian female population was also obtained from Statistics Austria.

The survival of our patients was estimated and summarized using the Kaplan-Meier method.¹³ After adjustment for age and calendar period, the patient mortality rates were compared with those of the general Austrian female population using relative survival methods.¹⁴ Calculations were made in SAS and SAS macros provided by Dickman *et al.*¹⁵ Differences between groups were analyzed using the Fisher's exact test and the Jonckheere-Terpstra test for testing an ordered alternative.

Results and Discussion

Our study includes 728 women with a median age of 28.7 years (interquartile range (IQR) 21.6–36.3 years) at manifestation of venous thromboembolism. Patients' characteristics are listed in Table 1. In 400 patients (55%), venous thromboembolism was secondary, i.e. following a triggering event. The median follow-up time, i.e. visit at our clinic for routine coagulation screening until December 2006 or death, respectively, was 14 years. Sixty-one percent of our patients received short-term oral anticoagulation with vitamin K antagonists after the first deep venous thrombosis or pulmonary embolism, a further 18% used oral contraceptives for 6-18 months and 18% had long-term anticoagulation. For 3% of the patients, data on the duration of oral contraceptives are not available.

During the entire analysis period of 22 years, a total of 23 patients (3.2%) died. Causes of death were cancer in 6 patients (26%), bleeding and thrombosis each in 2 (8.7%), heart disease in 4 (17.4%), and stroke in one patient (4.3%). Six patients (26%) died due to various other causes and for 2 patients (8.7%) the cause of death is not clearly defined due to vague coding in the ICD. The mean age at death was 57 years (IQR 52-70 years). The mean age of the surviving women was 48 years (IQR 40-57 years). Of those with short-term anticoagulation 13 patients (2.9%), of those with anticoagulation between 6-18 months one patient (0.8%), and of those with long-term anticoagulation 7 patients (5.5%) died. Statistical analysis of the different groups of oral contraceptive users did not show a significant difference with a *P* value of 0.0828 when using the Fisher's exact test and a *P* value of 0.536 when using the Jonckheere-Terpstra test.¹⁶

The cumulative relative survival of our patients in comparison to the general Austrian female population was 1.03 (95% confidence interval 0.99-1.04; Figure 1). Neither the subgroup of women with pulmonary embolism (cumulative relative survival 1.03, 95% CI 1.01-1.04) nor those with spontaneous (without a known triggering event) events (1.03, 95% CI 0.99-1.06) had a decreased survival in comparison to the general population. Our data show that long-term survival of young women with a history of venous thromboembolism does not differ from the survival of the general Austrian female population.

There are only few data on the long-term survival rate in patients following venous thromboembolism available. Schulman *et al.*⁷ reported on a 10-year death rate of 28.5%. This high mortality rate may be due to patients' characteristics, specifically the higher age at first venous thromboembolism (more than 50% over 60 years) and co-morbidities, such as cancer or cardiovascular diseases. A com-

parison to the general population or a population with similar co-morbidities was not performed.

Heit *et al.*¹⁷ reported an 8-year survival rate of 47.5% following venous thromboembolism. Patients from this cohort had a reduced survival in comparison to the residents of Minnesota due to a higher mortality in the first months. Interestingly, although patients with deep venous thrombosis and/or pulmonary embolism had a decreased survival in the first months after thrombosis, the survival curve of the patient cohort is parallel to the expected survival of Minnesota residents after approximately one year. Further important differences to our study are the presence of malignancies in the patient cohort and their higher age.

Naess *et al.*¹ estimated the mortality after venous thromboembolism for the population of Nord-Trøndelag and found a one year case fatality rate of 21.6% (12.6% in patients without cancer). They noted the highest risk of death during the first few months following venous thromboembolism; thereafter, the mortality rate in non-cancer patients gradually reached that of the general population. These results on long-term survival are comparable to our findings.

Recent data from the MEGA-study in the Netherlands¹⁸ show a 2-fold increased risk of death in patients without a malignancy following an episode of venous thromboembolism compared to the general population. Again, this study includes all patients under 70 years of age, which might also explain the differences to our findings.

Optimal duration of anticoagulation in patients with venous thromboembolism is still being discussed. Contrary to previous versions, in 2008 the American College of Chest Physicians (ACCP) recommended (grade 1A) long-term anticoagulation in those with a single episode of proximal deep venous thrombosis or pulmonary embolism, when no transient risk factors are present.¹⁹ These guidelines are based on interventional studies²⁰⁻²³ that clearly demonstrated the higher recurrence rate

Table 1. Patients' characteristics.

Site of VTE	Patient N./ Total patient N.	%
DVT leg – popliteal and calf veins	294/728	40.4%
DVT leg – femoral and ileal veins	139/728	19.1%
DVT leg and PE	111/728	15.2%
PE without detectable DVT	128/728	17.6%
DVT arm	23/728	3.2%
Others (portal vein thrombosis, splenic vein thrombosis, thrombosis of the vena cava, retinal vein thrombosis)	33/728	4.5%
Spontaneous VTE	328/728	45%
Triggering event		
Surgery	96/728	13.2%
Trauma	72/728	9.9%
Pregnancy	38/728	5.2%
Puerperium	63/728	8.7%
Cesarean section	19/728	2.6%
Abortion	5/728	0.7%
Immobilization	40/728	5.5%
Others	67/728	9.2%
Oral contraceptives	438/665	65.9%
Positive family history for VTE	274/728	37.6%

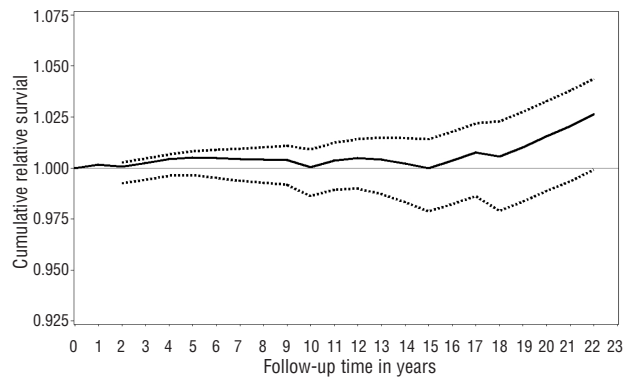


Figure 1. Cumulative relative survival of all patients. Continuous line cumulative relative survival, mean dotted line cumulative relative survival, upper and lower 95% CI straight, light line survival of the Austrian female population; reference line.

in patients, who had discontinued anticoagulation. Death rates given in these studies (below 6%) did not differ among patients with and without anticoagulation except for the study by Schulman *et al.*²³ who reported a higher death rate in patients with recurrent venous thromboembolism in whom warfarin had been stopped.

Our study shows no significant difference regarding survival considering different duration periods of oral contraceptive use. The largest proportion of patients died in the group with long-term anticoagulation. This might be due to their risk profile which, most probably, was actually the reason for the initial long-term anticoagulation.

Our study has several limitations. The most important one is the retrospective design. However, we included all women with venous thromboembolism who visited our department during a given time period, which can be seen as a strength of this study. The Austrian Death Register covers all deaths occurring within Austria. Since the ten-

dency to relocate in Austria is rather low, we are sure we have covered the vast majority of deaths. Moreover, our study shows a tendency towards better survival, so even if we had missed a small number of deaths the results would not change. However, in the majority of our patients a triggering event could be identified, which correlates to a lower risk profile. This might also explain the tendency for a better survival in our patient cohort. Another limitation is that our study does not cover the acute phase following venous thromboembolism; therefore, we are unable to draw any conclusions concerning short-term survival. However, this was actually not the aim of our study. Our data also cannot be applied to men or older patients; these groups have to be investigated separately. With regard to risk factors for venous thromboembolism, there might be some recall bias as patients were referred to our department some time after initial occurrence of venous thromboembolism.

In conclusion, our results show that in the long term, after the more critical initial period, venous thromboembolism does not influence survival of young women. Anticoagulation considerably influences the quality of life, and young women of childbearing age may fear the well-known embryotoxic effect. When deciding on treatment modalities, particularly long-term anticoagulation, the risk of fatal bleeding and other untoward effects should always be assessed versus the risk of fatal recurrent venous thromboembolism²⁴ which, according to our data, seems to be very low in young women.

Authorship and Disclosures

SER performed research, collected data, wrote the manuscript. CL designed and performed research, collected data. TW analyzed and interpreted data, performed statistical analysis. CV designed research and interpreted data. IP designed research and performed research, analyzed and interpreted data, wrote the manuscript.

The authors reported no potential conflicts of interest.

References

- Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerström J. Incidence and mortality of venous thrombosis: a population-based study. *J Thromb Haemost.* 2007;5(4):692-9.
- Anderson FA Jr, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. *Arch Intern Med.* 1991;151(5):933-8.
- Nordstrom M, Lindblad B, Bergqvist D, Kjellstrom T. A prospective study of the incidence of deep-vein thrombosis within a defined urban population. *J Intern Med.* 1992;232(2):155-60.
- Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet.* 1999;353(9162):1386-9.
- Kyrle PA, Eichinger S. Deep vein thrombosis. *Lancet.* 2005;365(9465): 1163-74.
- Kyrle PA, Minar E, Bialonczyk C, Hirschl M, Weltermann A, Eichinger S. The risk of recurrent venous thromboembolism in men and women. *N Engl J Med.* 2004; 350(25):2558-63.
- Schulman S, Lindmarker P, Holmström M, Lärfars G, Carlsson A, Nicol P, et al. Post-thrombotic syndrome, recurrence, and death 10 years after the first episode of venous thromboembolism treated with warfarin for 6 weeks or 6 months. *J Thromb Haemost.* 2006;4(4):734-42.
- García-Fuster MJ, Forner MJ, Fernández C, Gil J, Vaya A, Maldonado L. Long-term prospective study of recurrent venous thromboembolism in patients younger than 50 years. *Pathophysiol. Haemost Thromb.* 2005;34(1):6-12.
- Kniffin WD Jr, Baron JA, Barrett J, Birkmeyer JD, Anderson FA Jr. The epidemiology of diagnosed pulmonary embolism and deep venous thrombosis in the elderly. *Arch Intern Med.* 1994;154(8): 861-6.
- van Beek EJ, Kuijjer PM, Büller HR, Brandjes DP, Bossuyt PM, ten Cate JW. The clinical course of patients with suspected pulmonary embolism. *Arch Intern Med.* 1997;157(22):2593-8.
- Beyth RJ, Cohen AM, Landefeld CS. Long-term outcomes of deep-vein thrombosis. *Arch Intern Med.* 1995;155(10):1031-7.
- Prandoni P, Lensing AW, Cogo A, Cuppini S, Villalta S, Carta M, et al. The long-term clinical course of acute deep vein thrombosis. *Ann Intern Med.* 1996;125(1):1-7.
- Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. *J Am Stat Assoc.* 1958;53:457-81.
- Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. *Stat Med.* 2004;23(1):51-64.
- Dickman P. Estimating and modelling relative survival using SAS. 2004 Jun 19 Version 1.0 [cited 2009 Dec 1]. Available from: URL: http://www.pauldickman.com/rsmode/sas_colon/
- Jonckheere AR. A Distribution-Free Kappa-

- Sample Test Against Ordered Alternatives. *Biometrika*. 1954;41:133-45.
17. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd. Predictors of survival after deep vein thrombosis and pulmonary embolism - A population-based, cohort study. *Arch Intern Med*. 1999;159(5):445-53.
 18. Flinterman LE, van Hylckama Vlieg A, Cannegieter SC, Rosendaal FR. Mortality and recurrence after a first venous thrombosis. ISTH Boston, 2009. Abstract OC-MO-079.
 19. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ; American College of Chest Physicians. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133(6 Suppl):454S-545S.
 20. Kearon C, Gent M, Hirsh J, Weitz J, Kovacs MJ, Anderson DR, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med*. 1999;340(12):901-7.
 21. Agnelli G, Prandoni P, Becattini C, Silingardi M, Taliani MR, Miccio M, et al. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. *Ann Intern Med*. 2003;139(1):19-25.
 22. Agnelli G, Prandoni P, Santamaria MG, Bagatella P, Iorio A, Bazzan M, et al. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. *N Engl J Med*. 2001;345(3):165-9.
 23. Schulman S, Granqvist S, Holmström M, Carlsson A, Lindmarker P, Nicol P, et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. The Duration of Anticoagulation Trial Study Group. *N Engl J Med*. 1997;336(6):393-8.
 24. Palareti G, Cosmi B, Legnani C, Tosetto A, Brusi C, Iorio A, et al. D-dimer testing to determine the duration of anticoagulation therapy. *N Engl J Med*. 2006;355(17):1780-9.