

INCIDENCE OF CANCER AFTER PROPHYLAXIS WITH WARFARIN AGAINST RECURRENT VENOUS THROMBOEMBOLISM

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ABSTRACT

Background The length of time after an episode of venous thromboembolism during which the risk of newly diagnosed cancer is increased is not known, and whether vitamin K antagonists have an antineoplastic effect is controversial.

Methods In a prospective, randomized study of the duration of oral anticoagulation (six weeks or six months) after a first episode of venous thromboembolism, patients were questioned annually about any newly diagnosed cancer. After a mean follow-up of 8.1 years, we used the Swedish Cancer Registry to identify all diagnoses of cancer and causes of death in the study population. The observed numbers of cases of cancer were compared with expected numbers based on national incidence rates, and the standardized incidence ratios were calculated.

Results A first cancer was diagnosed in 111 of 854 patients (13.0 percent) during follow-up. The standardized incidence ratio for newly diagnosed cancer was 3.4 (95 percent confidence interval, 2.2 to 4.6) during the first year after the thromboembolic event and remained between 1.3 and 2.2 for the following five years. Cancer was diagnosed in 66 of 419 patients (15.8 percent) who were treated for six weeks with oral anticoagulants, as compared with 45 of 435 patients (10.3 percent) who were treated for six months (odds ratio, 1.6; 95 percent confidence interval, 1.1 to 2.4). The difference was mainly due to the occurrence of new urogenital cancers, of which there were 28 cases in the six-week group (6.7 percent) and 12 cases in the six-month group (2.8 percent) (odds ratio, 2.5; 95 percent confidence interval, 1.3 to 5.0). The difference in the incidence of cancer between the treatment groups became evident only after two years of follow-up, and it remained significant after adjustment for sex, age, and whether the thromboembolism was idiopathic or nonidiopathic. Older age at the time of the venous thrombosis and an idiopathic thromboembolism were also independent risk factors for a diagnosis of cancer. No difference in the incidence of cancer-related deaths was detected.

Conclusions The risk of newly diagnosed cancer after a first episode of venous thromboembolism is elevated during at least the following two years. Subsequently, the risk seems to be lower among patients treated with oral anticoagulants for six months than among those treated for six weeks. (N Engl J Med 2000;342:1953-8.)

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THE incidence of cancer is increased during the first year after the diagnosis of venous thromboembolism and may also be increased, to a lesser extent, for at least the next 10 years, as shown in large cohort studies of data from registries.^{1,2} A prospective study has shown that the risk of subsequent cancer is higher among patients with idiopathic deep-vein thrombosis than among those with an identified triggering factor.³

Warfarin therapy was reported to improve the survival of patients with small-cell lung cancer in a prospective clinical trial in 1981,⁴ but this finding has never been confirmed. Conversely, in another trial, patients with this type of cancer who received chemotherapy and radiation did not have an improved outcome when warfarin was added to their treatment.⁵ Retrospective studies of patients treated with various vitamin K antagonists exclusively⁶ or mainly^{7,8} for cardiac disease did not convincingly show a reduced incidence of cancer⁶ or of death related to cancer,^{7,8} but the numbers of events were low,^{6,7} and selection bias may have distorted the results.

In this prospective study of patients with an objectively verified first episode of venous thromboembolism who were randomly assigned to receive treatment with vitamin K antagonists for six weeks or six months, we determined the incidence of newly diagnosed cancer for a period of six to nine years. Our primary aim was to assess, in a retrospective analysis of prospectively collected data, the length of time after a thromboembolic event during which the incidence of cancer is increased.

METHODS

Study Design

From April 1988 to April 1991, 902 consecutive patients at least 15 years of age with an objectively verified first episode of deep-vein thrombosis in a leg or a first episode of symptomatic pulmonary embolism were randomly assigned to receive prophylaxis with vitamin K antagonists for either six weeks or six months.⁹ The study was carried out at 16 hospitals in central Sweden. Patients in whom cancer had been diagnosed at any time before randomization, according to information from the patient's history and from medical records available to the investigator, were excluded from the study. Oral anticoagulant therapy consisted of warfarin sodium (Waran, Nycomed, Oslo, Norway) in 854 patients and dicumarol (Apekumarol, Ferrosan, Malmö, Sweden) in 48 patients and was usually started at the same time as the heparin therapy.

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Oral anticoagulation was targeted to achieve an international normalized ratio (INR) of 2.0 to 2.85. No general screening for cancer was performed, but at the discretion of the investigator specific tests could be performed if warranted by symptoms or signs.

The patients were followed at annual clinical visits, at which time the investigator or research nurse questioned them about the occurrence of cancer. The report of a diagnosis of cancer from a patient was checked against medical records from the clinic where the cancer had been diagnosed. In cases of death, the cause was investigated by a review of hospital records and autopsy reports. The status of patients lost to follow-up was checked at intervals with the Death Registry in Sweden, so that no instances of death would be missed.

To ascertain that information about cases of newly diagnosed cancer had not been missed, data from the national Swedish Cancer Registry, founded in 1958, was also obtained for follow-up through December 1997. The mean duration of follow-up was thus 8.1 years (range, 6.6 to 9.6). For calculations of relative risks and life-table analyses, data on diagnosed cancers were censored at six years of follow-up in order to minimize the effect of any delayed reporting to the Swedish Cancer Registry. However, data on deaths from cancer were available until April 1999 and were therefore censored at eight years. The study was approved by the regional ethics committee of the Karolinska Institute and by the Swedish Data Inspection Board. The patients provided informed consent for treatment with anticoagulants.

Statistical Analysis

For each year of follow-up, the expected numbers of new cancers were calculated by multiplying the number of patients studied by the appropriate nationwide sex- and age-specific incidence rates (with use of five-year age groups) as provided by the Swedish Cancer Registry. Relative risks were expressed as standardized incidence ratios, which are the ratios of observed numbers of new cancers to the numbers expected. Any case of newly diagnosed cancer was included in the analysis. Ninety-five percent confidence intervals for a binomial distribution were calculated. Life-table analyses were based on the first primary cancer diagnosed. In the multivariate analysis, all variables that yielded a *P* value of less than 0.3 in the univariate analysis were entered. A Cox proportional-hazards model was used in the multivariate analysis, which was performed with JMP 3.1 software (SAS Institute, Cary, N.C.).

RESULTS

Five of the 902 patients were withdrawn from the study almost immediately because a congenital deficiency of protein C was detected. The characteristics of the remaining 443 and 454 patients randomly assigned to six weeks and six months, respectively, of treatment with vitamin K antagonists were similar.⁹ The actual duration of treatment was 1.5 months in the six-week group and 6.0 months in the six-month group after the initial thromboembolic event; additional treatment for a mean of 4.9 and 3.4 months, respectively, was given for recurrent events throughout the period of follow-up.

According to data from the Swedish Cancer Registry, 43 of the 897 patients (4.8 percent) had received a diagnosis of cancer before inclusion in the study; 2 of these cases became known to the investigators during follow-up. The mean interval between the diagnosis and the venous thromboembolic event was 13 years (range, 0 to 29). Sixteen of 43 patients had carcinoma *in situ* of the cervix, and 5 had nonmelanoma skin tumors; the other 22 patients had more

advanced cancers. When these 43 patients were included in the analysis, there were 74 patients in whom cancer was diagnosed after the thromboembolic event among the 443 patients assigned to anticoagulation for six weeks (16.7 percent) and 47 among the 454 patients assigned to anticoagulation for six months (10.4 percent) (odds ratio, 1.7; 95 percent confidence interval, 1.2 to 2.6). However, the 43 patients with a previous diagnosis of cancer were excluded from all further analyses.

Of the 854 patients who constituted the final study population, we identified 111 patients (13.0 percent) who received a first diagnosis of cancer during a mean follow-up of 8.1 years after the first episode of venous thromboembolism. For 17 of the 111 patients (15.3 percent), the cancer was not identified during the clinical follow-up, and for 24 (21.6 percent) the diagnosis was not reported to the Swedish Cancer Registry. The age- and sex-matched standardized incidence ratios for cancer were 3.4 during the first year after the first episode of venous thromboembolism and 1.9 during the second year. The standardized incidence ratios also remained greater than 1 during the next four years, but for most of those years the 95 percent confidence interval extended below 1 (Fig. 1). In the univariate analysis there were significantly more cases of newly diagnosed cancer among patients assigned to six weeks of anticoagulation than among those assigned to six months of anticoagulation (*P*=0.02) (Table 1). The main types of cancer diagnosed in the two groups are shown in Table 1. There was a significant difference between the groups in the incidence of urogenital cancers (cancers of the kidney, urinary bladder, prostate, ovary, and uterus).

The cumulative probability of a diagnosis of cancer during six years of follow-up is shown in Figure 2. During the third year after the episode of venous thromboembolism and the start of anticoagulant therapy, the difference between the groups in the probability of a diagnosis of cancer became evident, and this difference became increasingly pronounced during each of the following three years. When only the cancers diagnosed after two years are taken into account, the difference between the groups in the incidence of new urogenital cancers was even more pronounced, with 19 cases among those treated for six weeks and 5 among those treated for six months (*P*=0.004). Cancer of the prostate was diagnosed in 17 and 9 patients, respectively, over the entire follow-up period and in 12 and 4 patients during follow-up after the first two years. In only one of these patients was the diagnosis made by screening for cancer after a recurrence of venous thromboembolism.

The standardized incidence ratios for cancer according to the duration of treatment with vitamin K antagonists are shown in Figure 3 for six years of follow-up. During this period the incidence of newly diagnosed cancer in the six-month group was lower

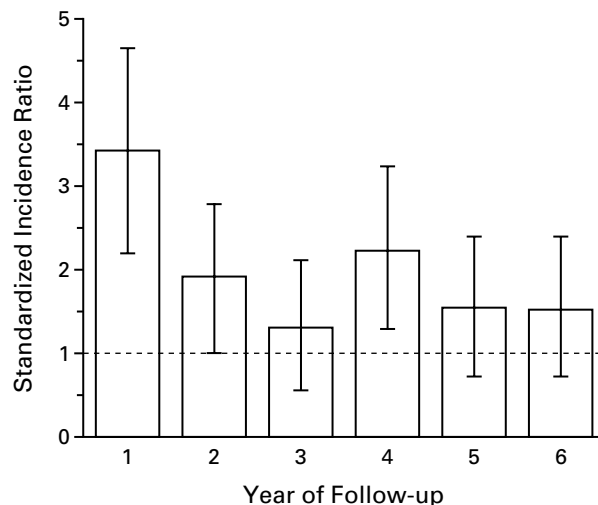


Figure 1. Standardized Incidence Ratios for Newly Diagnosed Cancer after a First Episode of Venous Thromboembolism. I bars represent 95 percent confidence intervals.

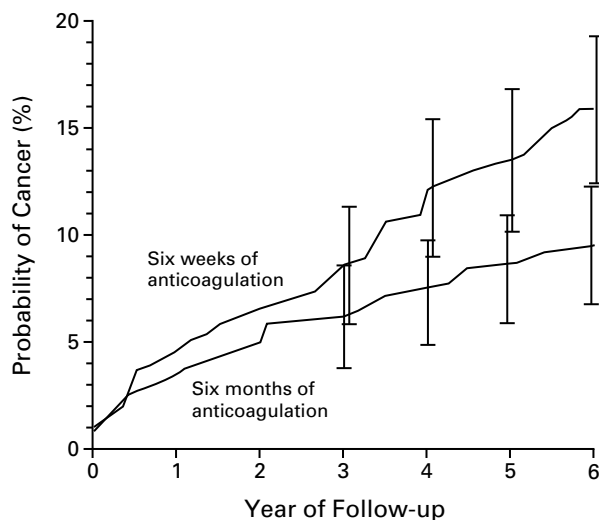


Figure 2. Cumulative Probability of Newly Diagnosed Cancer after a First Episode of Venous Thromboembolism. I bars represent 95 percent confidence intervals.

TABLE 1. INCIDENCE OF NEWLY DIAGNOSED CANCER AFTER A FIRST EPISODE OF VENOUS THROMBOEMBOLISM, ACCORDING TO THE DURATION OF ANTICOAGULANT THERAPY.*

VARIABLE	DURATION OF ANTICOAGULANT THERAPY		ODDS RATIO (95% CI)	P VALUE
	6 WK (N=419)	6 MO (N=435)		
	no. of patients (%)			
Any cancer	66 (15.8)	45 (10.3)	1.6 (1.1–2.4)	0.02
Type of cancer				
Respiratory tract	9 (2.1)	6 (1.4)		NS
Gastrointestinal	12 (2.9)	11 (2.5)		NS
Urogenital†	28 (6.7)	12 (2.8)	2.5 (1.3–5.0)	0.01
Hematologic	8 (1.9)	7 (1.6)		NS
Dermatologic	6 (1.4)	3 (0.7)		NS
Other	3 (0.7)	6 (1.4)		NS

*CI denotes confidence interval, and NS not significant.
 †Urogenital cancers comprised cancers of the kidney, urinary bladder, prostate, ovary, and uterus.

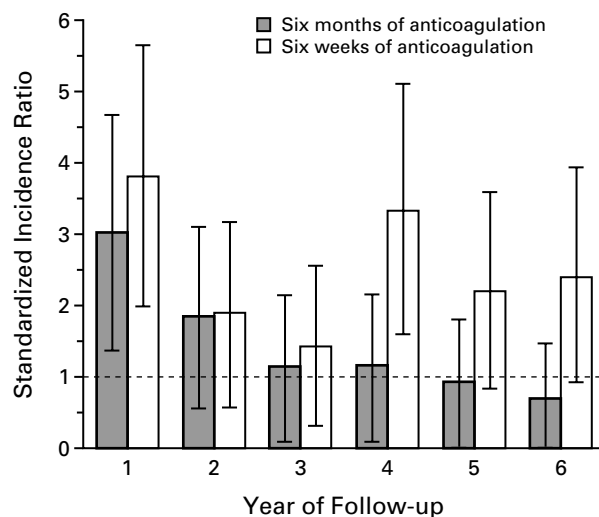


Figure 3. Standardized Incidence Ratios for Newly Diagnosed Cancer after a First Episode of Venous Thromboembolism, According to the Duration of Treatment with Vitamin K Antagonists. I bars represent 95 percent confidence intervals.

than that in the six-week group, but this difference was not mirrored by a lower rate of death due to cancer during eight years of follow-up (data not shown). No instances of death during follow-up were missed.

We also calculated the standardized incidence ratios for cancer in subgroups of patients according to whether the venous thromboembolism was idiopathic (i.e., there was no identified cause or there was venous insufficiency at the time of the initial thrombotic event, without previous thrombosis) or nonidiopathic (i.e., it was associated with a temporary trig-

gering factor, such as surgery, trauma, temporary immobilization, or use of oral contraceptives). As shown in Figure 4, the standardized incidence ratios for the subgroup of 534 patients with idiopathic thromboembolism were similar to those for the entire study population (Fig. 1), whereas the standardized incidence ratios for the subgroup of 320 patients with nonidiopathic thromboembolism had a less well de-

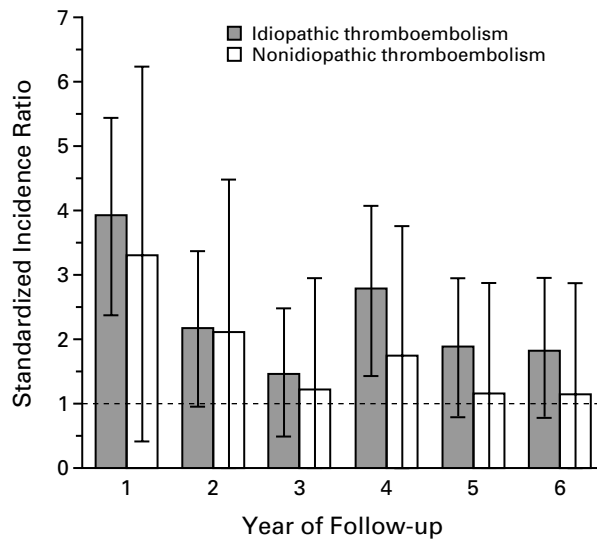


Figure 4. Standardized Incidence Ratios for Newly Diagnosed Cancer after a First Episode of Venous Thromboembolism, According to Whether the Thromboembolism Was Idiopathic or Nonidiopathic.

I bars represent 95 percent confidence intervals.

finer pattern, with wide confidence intervals because of the smaller numbers of patients in this subgroup. A difference between the two subgroups in the cumulative probability of cancer became evident very early and became increasingly pronounced during six years of follow-up (Fig. 5). Within the subgroup of patients with nonidiopathic venous thromboembolism, the difference in the cumulative probability of a cancer diagnosis between the patients assigned to six weeks of anticoagulant treatment and those assigned to six months did not reach statistical significance at any time.

In a multivariate analysis of the incidence of newly diagnosed cancer during six years of follow-up, with adjustment for the origin of the thromboembolism (idiopathic or nonidiopathic), recurrence or nonrecurrence of the thromboembolism during follow-up, sex, and age, the risk ratio was 1.3 for the group assigned to treatment for six weeks as compared with the group assigned to treatment for six months (95 percent confidence interval, 1.1 to 1.6; $P=0.005$). Older age at the time of enrollment and idiopathic venous thromboembolism were also independent risk factors for a new diagnosis of cancer, with odds ratios of 1.1 (95 percent confidence interval, 1.0 to 1.1; $P<0.001$) for each additional year of age and 1.5 (95 percent confidence interval, 1.2 to 2.0; $P<0.001$) for idiopathic venous thromboembolism. As compared with patients who did not have a recurrent thromboembolism, those with a recurrence had a risk ratio of 1.3 (95 percent confidence interval, 1.0 to 1.6; $P=$

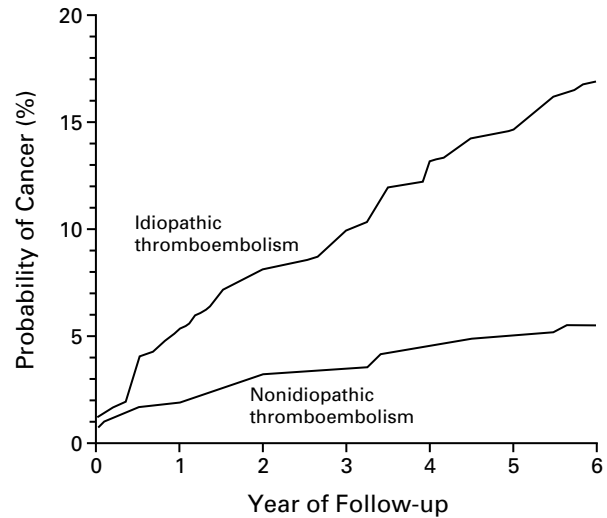


Figure 5. Cumulative Probability of Newly Diagnosed Cancer after a First Episode of Venous Thromboembolism, According to Whether the Thromboembolism Was Idiopathic or Nonidiopathic.

0.02). Sex, the type of thromboembolic event (deep-vein thrombosis or pulmonary embolism), the presence of antibodies against cardiolipin, and impaired fibrinolytic activity were not predictors of a new diagnosis of cancer in this model.

DISCUSSION

The protocol for this multicenter trial comparing six weeks with six months of oral anticoagulation initially specified a follow-up of two years. Since there were more patients enrolled in our study than in most randomized studies of the treatment of venous thromboembolism, we realized that it would be important to extend the duration of follow-up. Questioning of the patients about any newly diagnosed cancer was part of the initial protocol, but the impression that this type of communication between patients and research nurses was sometimes difficult led us to obtain this information from the Swedish Cancer Registry. Neither of these sources turned out to be flawless. Approximately 3 percent of all actual diagnoses of cancer may have been missed in our study.

Another weakness of this study is that its size was not planned for the purpose of comparing the risk of new cancers in the two treatment groups, since the primary end point of the trial was recurrent venous thromboembolism. Nevertheless, the two treatment groups were similar in all respects at the time of randomization, and they were followed prospectively thereafter. Since more patients in the six-week group than in the six-month group had recurrent venous

thromboembolism and thus reached an end point, with subsequent discontinuation of clinical follow-up and ascertainment of diagnoses of cancer, the true difference between the groups in the incidence of cancer may be even greater. It is unlikely that more intense screening for cancer in the six-week group than in the six-month group (because of the greater number of recurrent thromboembolic events in the six-week group) is the reason for their higher incidence of cancer in the six-week group, since the difference in the rate of recurrent events was restricted to the period between 1.5 and 6 months after the initial event⁹ and since the difference in the incidence of cancer was found between 2 and 6 years.

The part of our study that analyzed standardized incidence ratios for cancer after venous thromboembolism is not original, since two large, retrospective, registry-based studies of this issue were published in 1998.^{1,2} The advantage of our results is that they were obtained in a prospective study in which venous thromboembolism was always confirmed objectively. In our searches of medical records in the Swedish Inpatient Register, which is the same registry used in one of the previous studies,¹ we found that the diagnoses "deep-vein thrombosis" and "pulmonary embolism" were coded incorrectly in 10 to 20 percent of the registry cases. However, the long-term increase in the risk of cancer after venous thromboembolism, demonstrated in the study by Baron et al.¹ and less convincingly in the smaller study by Sørensen et al.,² is supported by the results of our even smaller but better-defined and more homogeneous population, with consistent trends observed for years 3 through 6 of follow-up. Moreover, the cases of new cancers observed in our study were identified on the basis of two complementary types of information — patients' responses to questions and registry data — whereas the numbers of expected cases were based only on the latter; thus, a small portion of the difference we noted between the observed and expected incidence of cancer, expressed as the standardized incidence ratio (Fig. 1), may be an overestimate.

Our findings strongly support the impression that warfarin has an antineoplastic effect,⁴ but this idea will remain controversial in the absence of a demonstrated biochemical explanation. The reason this effect was observed two years after the initial thrombotic event and not earlier could be that the effect is exerted mainly on small cancers and not on those already of a size amenable to diagnosis. The lack of an effect of the duration of anticoagulation on the rate of death from cancer may be due to insufficient follow-up, since, for example, the survival of patients with cancer of the prostate is relatively long. A contributing explanation is that some of the cancers suppressed by vitamin K antagonists, such as the dermatologic cancers, might have been curable. The reason we detected a significant difference between the six-

week group and the six-month group only in the incidence of urogenital cancers is difficult to explain, unless it is purely a result of larger numbers for this type of cancer, since cancer of the prostate was by far the most common neoplasm in our population.

Whether the positive effect of prolonged anticoagulation with vitamin K antagonists will eventually have an effect on cancer-related mortality or whether the treatment merely postpones the clinical presentation of cancer and there will be an increased incidence later on is a question that can be solved only in large, randomized trials with even longer periods of follow-up.

An antineoplastic effect of vitamin K antagonists could be mediated by an effect on the pathway involving tissue factor and factor VIIa, with subsequent down-regulation of the expression of urokinase receptors and inhibition of tumor invasion.¹⁰ Alternatively, it may be mediated by other vitamin K–dependent coagulation factors; for example, inhibition of the generation of thrombin by warfarin may decrease the thrombin-induced release of matrix metalloproteinase 2 and thereby hinder the breakdown of extracellular matrix proteins.¹¹ It will be important to sort out these mechanisms and to assess the possible antineoplastic effect of antithrombotic agents through large studies with long follow-up periods.

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APPENDIX

The Duration of Anticoagulation Trial involved the following investigators and institutions, all of which are in Sweden (with the principal investigator listed first for each institution): Danderyd Hospital, Danderyd: A. Carlsson; Huddinge Hospital, Huddinge: A.-S. Rhedin, M. Holmström, and D. Lockner; Karolinska Hospital, Stockholm: S. Schulman, P. Lindmarker, and H. Johnsson; Köping Hospital, Köping: P. Nicol, J. Kobosko, B. Malmros, N. Arcini, and J. Saaw; Nacka Hospital, Stockholm: E. Loogna and R. Stig; Norrtälje Hospital, Norrtälje: S. Viering; Nyköping Hospital, Nyköping: B. Ljungberg and S. Wilhelmsson; Sabbatsberg Hospital, Stockholm: H. Walter, K. Malmqvist, and E. Al-Khalili; St. Göran Hospital, Stockholm: B. Leijd and A. Petrescu; Södersjukhuset, Stockholm: J. Brohult and G. Lärffars; Södertälje Hospital, Södertälje: S.-G. Eklund, E. Svensson, and L. Dahlin; Uppsala Academic Hospital, Uppsala: J. Boberg; Västerås Central Hospital, Västerås: S. Nordlander and B. Marjanovic; Örebro Regional Hospital, Örebro: O. Linder; Linköping Regional Hospital, Linköping: K.-Å. Jönsson and C. Malm; and Lidköping Hospital, Lidköping: M. Hjorth and A. Lindgren.

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