Clinical and biochemical risk factors for first and recurrent episodes of venous thrombosis

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Chapter 2.1

Incidence and mortality of venous thrombosis: a population-based study

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Summary

Background: Estimates of the incidence of venous thrombosis (VT) vary, and data on mortality are limited.

Objectives: We estimated the incidence and mortality of a first VT event in a general population.

Methods: From the residents of Nord-Trøndelag county in Norway aged 20 years and older (n=94,194), we identified all cases with an objectively verified diagnosis of VT that occurred between 1995 and 2001. Patients and diagnosis characteristics were retrieved from medical records.

Results: Seven hundred and forty patients were identified with a first diagnosis of VT during 516,405 person-years of follow-up. The incidence rate for all first VT events was 1.43 per 1000 person-years [95% confidence interval (CI): 1.33-1.54), that for deep-vein thrombosis (DVT) was 0.93 per 1000 person-years (95% CI: 0.85-1.02), and that for pulmonary embolism (PE) was 0.50 per 1000 person-years (95% CI: 0.44-0.56). The incidence rates increased exponentially with age, and were slightly higher in women than in men.
The 30-day case-fatality rate was higher in patients with PE than in those with DVT [9.7% vs. 4.6%, risk ratio 2.1 (95% CI: 1.2-3.7)]; it was also higher in patients with cancer than in patients without cancer [19.1% vs. 3.6%, risk ratio 3.8 (95% CI: 1.6-9.2)]. The risk of dying was highest in the first months subsequent to the VT, after which it gradually approached the mortality rate in the general population.

Conclusions: This study provides estimates of incidence and mortality of a first VT event in the general population.

Introduction

Venous thrombosis (VT) is the third most common cardiovascular disease after myocardial infarction [1,2] and stroke [3]. In the Western parts of the world, which have increasingly older populations, VT is a major health problem. The estimated incidence rates for VT vary between 1 and 2 per 1000 person-years [4-10]. In addition to real differences, variations in these estimates may also depend on the study design, case definition, and age distribution.
VT has genetic and acquired risk factors. Knowledge of the latter is important for prevention purposes. For example, a large proportion of cases is related to surgery (around 20%), which has a 6-fold increased risk of VT [5,11].
Reports on mortality after VT are scarce, and the estimates vary considerably. Reports of 30-day and 90-day case fatality rates have varied from less than 10% to 30% [5,12-20], and reports on 1-year case-fatality rates vary even more [4,15,21-23]. Many of these studies were randomized clinical studies [12,14,17,19,22], which are often based on selected groups of patients. Cohort studies [4,5,13,15,16,18] often included thromboses diagnosed by autopsy, and thus both the incidence rates and mortality rates were influenced by different autopsy rates.
Studies based on data from national registries suggest an increase in admission rates and mortality from VT after 1990 [24,25]
We estimated the incidence and mortality of a first VT event in the total population in the county of Nord-Trøndelag, in central Norway. We used validated VT diagnoses from hospital discharge registries linked to data from the HUNT2 study. These data provide a basis for both health care planning and future research on VT.

Materials and methods

The study population
The study population included all residents aged 20 years or more (n = 94,194) in Nord-Trøndelag county in central Norway in 1995-1997. During 1995-1997, all inhabitants of this county were invited to participate in a large-scale general health study (the HUNT2 study) [26]
We were provided with a database of the HUNT2 population. The population of Nord-Trøndelag is ethnically homogeneous (97% Caucasian), and the county is fairly representative of Norway with regard to geography, economy, industry, age distribution, morbidity, and mortality [http://www.ssb.no]. The population has low geographic mobility, and is served by a centralized health service. It is thus well suited for a population study with follow-up. The median age of the invited individuals was 46 years, ranging from 20 to 103 years.

Case identification
We identified all individuals registered with a diagnosis of VT, i.e. deep-vein thrombosis (DVT) or pulmonary embolism (PE), in the Nord-Trøndelag County from 1 January 1995 to 31 December 2001, by means of the electronic patient registry from the only two hospitals in the county, Levanger and Namsos Hospital. We identified inpatients and outpatients from all departments on the basis of International Classification of Disease, Ninth and Tenth Revision (ICD-9 and ICD-10) discharge diagnostic codes for DVT and PE (see Appendix).

We also identified positive diagnostic procedure codes for venography, duplex ultrasound and Doppler ultrasound from the two radiologic departments in the two hospitals. No radiology service was offered outside the hospitals. Finally, we performed a case-finding search at the tertiary-care center of the region, St Olav Hospital, Trondheim University Hospital, in the neighbouring county for residents of Nord-Trøndelag county discharged with a diagnostic code of VT.

Two physicians (I. A. Næss, S. C. Christiansen) reviewed the hospital records and validated each case. Adjudication differences were resolved by a consensus procedure. Each episode of VT or PE was categorized into three levels of diagnostic certainty (definite, probable and possible) on the basis of models used in other studies [5,9] and the 1995 revised PIOPED criteria [27,28]. Clinical diagnosis with no confirmatory test or with an indeterminate result was classified as possible VT and not included in the analyses. Definite DVT was defined by an intraluminal filling defect on ascending contrast venography in the leg or arm, a non-compressible venous segment in the popliteal, femoral or axillar veins on duplex ultrasound, or a positive computed tomography (CT) scan. Probable DVT required no venous filling on ascending contrast venography in the leg or arm or no venous flow in the popliteal, femoral or axillar veins on duplex ultrasound. Leg thrombosis was classified as proximal when the proximal extension was localized in the popliteal, femoral or iliac veins, and as distal when the thrombus was localized in the calf only (below the popliteal vein, diagnosed by venography). Upper-extremity thrombosis included thrombosis of arm veins, the superior vena cava, or the internal jugular, subclavian or axillary veins.

Definite PE was defined according to the PIOPED criteria [27,28] as a high-probability ventilation/perfusion (V/Q) scan, i.e. ≥ 2 segmental perfusion defects (V/Q mismatch), a perfusion scan with ≥ 2 segmental perfusion defects associated with normal chest X-ray (X/Q mismatch), or a positive CT scan. Probable PE was defined as an intermediate-probability V/Q scan (one moderate or large V/Q mismatch) or a positive echocardiogram/transesophageal echocardiogram.

Thrombosis events were classified as first or recurrent and secondary non-cancer, secondary cancer, or idiopathic. An event was regarded as secondary non-cancer VT when any of the following was registered in the medical record: trauma, surgery, marked immobility (specified as paresis, paralysis, prolonged bedrest because of an acute medical illness, or > 8 h travel) within the last 3 months, pregnancy or puerperium at the time of the event, or oral contraceptives used at the time of the event or up to 1 month before the event. An event was classified as secondary cancer VT when an active malignancy was registered at the event or within 6 months after the event. An event was considered idiopathic when none of the precipitating factors for a secondary VT was registered in the patient history.

Statistical analysis

The study population was followed from the date of entry until the event, emigration, death or end of follow-up, whichever occurred first. The end of follow-up was 31 December 2001 in the incidence analyses and 1 April 2004 in the case-fatality and mortality analyses. We used the unique person identification number assigned to every citizen in the country to link the study population to the death registry of Statistics Norway, which is a virtually complete and continuously updated register of all deaths and emigrations in Norway.

We used the observed number of cases of first VT as the numerator and the sum of individual person-time contributed by the total resident population of the area covered by the data (Nord-Trøndelag County) as the denominator to calculate incidence rates of first VT event.
Five-year age-specific and sex-specific incidence rates were calculated using achieved age during follow-up. Thus, each person contributed person-time in different age categories while aging during follow-up.
Incidence rates for VT, DVT and PE were standardized by using the direct method, applying the age-specific rates in each 5-year age group to the world (Segi) standard population aged 20 years and above (http://seer.cancer.gov).
We used first events of VT as the denominator and deaths from any cause after the event as the numerator to calculate case fatality.
We used the Kaplan-Meyer method to evaluate crude survival, and Cox regression with VT entered as a time-dependent covariate to study age-adjusted and sex-adjusted hazard ratios for mortality. VT cases were followed-up as non-VT cases until the event occurred, after which they were followed as VT cases. To assess the proportional hazard assumption, we used a log minus log plot.
Data were processed in SPSS for Windows version 12.0 (SPSS Inc., Chicago, IL, USA) and STATA version 9.0 (StataCorp, College Station, TX, USA).

Ethics
The study was approved by the National Data Inspectorate and the Regional Ethical Committee. Informed consent was obtained from all participants.

Results

Cohort
Of the 94,194 inhabitants over 20 years of age living in Nord-Trøndelag between 1995 and 1997, we excluded four persons who were found to reside outside the county, and 421 persons who were registered with VT before the start of follow-up. Thus, we included 93,769 subjects, yielding 516,405 person-years at risk for a first VT event, and 705,558 person-years for the survival analysis.

Cases
Of the 2,136 patients for whom discharge records were identified, 421 were excluded from the study because they had had a VT before entry, and 189 because they did not belong to the cohort (i.e. not residing in the county or less than 20 years of age at date of entry). Patients not identified as VT cases in the validation procedure (n = 497), patients with possible VT (n = 150), patients with eye thrombosis (n = 107) and patients diagnosed post-mortem only (autopsy) (n = 32) were excluded as cases, but contributed person-time in the follow-up (Fig. 1).
The characteristics of the 740 included patients with a first VT event are given in Table 1. There were 411 women and 329 men, with a median age of 75 and 71 years, respectively. Two-thirds (n = 482) of the patients had DVT and one-third (n = 211) had PE alone. Six per cent of the patients (n = 47) had concurrent DVT and PE, and were classified as having PE in the analyses.

Fifty-seven percent of the VTs in the leg were localized in the left leg (n = 260), 42% were localized in the right leg (n = 194), and 1% (n = 3) were bilateral; three-quarters (n = 328) were proximal, and one-quarter (n = 128) were distal. Approximately half of the patients with PE (142 of 258) had a bilateral or central thrombus (Table 1). The acquired risk factors are given in Table 2.

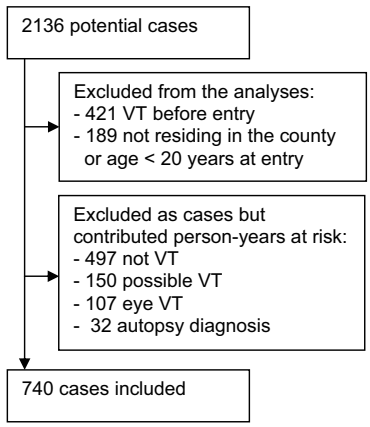

Figure 1. Case identification

Table 1: Characteristics of 740 patients with first VT events.

	Risk groups Idiopathic, n (%)	Secondary non-cancer, n (%)	Secondary cancer, n (%)	All, n (%)
DVT	234 (63)	155 (66)	93 (71)	482 (65)
PE	139 (37)	81 (34)	38 (29)	258 (35)
Total VT	373 (100)	236 (100)	131 (100)	740 (100)
Women	210 (56)	137 (58)	64 (49)	411 (56)
Median age in years (range)[1]	74.3 (25-102)	69.1 (22-91)	75.6 (32-95)	73.2 (22-102)
Location				
PE unilateral	59 (16)	37 (16)	20 (15)	116 (16)
PE bilateral/central	80 (21)	44 (19)	18 (14)	142 (19)
DVT arm	3 (1)	7 (3)	3 (2)	13 (2)
DVT central[2]	5 (1)	0	7 (5)	12 (2)
DVT leg	226 (61)	148 (63)	83 (63)	457 (62)
Distal leg	59 (26)	60 (40)	9 (11)[3]	128 (28)[3]
Proximal leg	167 (74)	88 (60)	73 (89)[3]	328 (72)[3]

DVT, deep vein thrombosis; PE, pulmonary embolism; VT, venous thrombosis.
[1] Age at event
[2] Vena lienalis (n = 3), vena mesenterica (n = 3), vena porta (n = 3), vena cava superior (n = 3), vena sagitalis superior (n = 2), vena cava inferior (n = 1), vena renalis (n = 1). Two of the cases had three locations.
[3] In one DVT patient, leg distal or proximal location was not specified.

Table 2: Acquired risk factors for venous thrombosis in 740 cases.

Risk factor	n	(%)
Surgery	148	(20)
Trauma	91	(12)
Marked immobility	77	(10)
Other*	18	(2)
Pregnancy/puerperium	13	(30)†
Oral contraceptives	7	(16)†
Active cancer	131	(18)
None (idiopathic)	373	(50)

Some of the cases had more than one risk factor.
*Tumor obstruction, central vein catheter, vessel anomaly.
†Among women < 45 years (n=43).

Incidence of first VT

The age-specific and sex-specific incidence rates are shown in Tables 3 and 4. The incidence rate of a first event of VT was 1.43 per 1000 person-years [95% confidence interval (CI): 1.33-1.54].

For DVT alone, the incidence rate was 0.93 per 1000 person-years (95% CI: 0.85-1.02), and for PE with or without DVT the estimated rate was 0.50 per 1000 person-years (95% CI: 0.44-0.56). The incidence rates increased exponentially with age. Incidence rates in subjects aged 70 years or above were more than three times higher than those in subjects aged 45-69 years, which again were three times higher than the rates in subjects aged 20-44 years. Women had an incidence rate of VT of 1.58 per 1000 person-years (95% CI: 1.44-1.74), as compared with 1.28 per 1000 person-years (95% CI: 1.15-1.43) in men. The incidence rate ratio was 1.2 (95% CI: 1.1-1.4) in women vs. men, but this difference disappeared in an age-adjusted analysis [incidence rate ratio 1.0 (95% CI: 0.9-1.2)]. During childbearing years, the incidence rate in women was twice the rate of incidence in men, but after 60 years, the rate was slightly higher in men.

The standardized incidence rate (world standard population) of a first event of VT was 0.94 per 1000 person-years (95% CI: 0.86-1.01), that for DVT alone was 0.61 per 1000 person-years (95 % CI: 0.55-0.67), and that for PE with or without DVT was 0.33 per 1000 person-years (95% CI: 0.28-0.37).

Case fatality and mortality

Table 5 shows the 30-day and 1-year case-fatality rates after a first VT event. During these periods, 47 and 160 people died, respectively. The most frequent causes of the 47 deaths within 30 days after the event were cancer (43%), PE (28%), cardiac death (13%), infection (8%), central VT (2%), and sudden death (2%). The cause of death was unknown in 4%. Among non-cancer VT patients, 45% of the deaths within 30 days were because of PE. The 30-day case-fatality rate was twice as high in patients with PE as in patients with DVT [9.7% vs. 4.6%; risk ratio 2.1 (95% CI: 1.2-3.7)]. In patients without cancer, this difference was of similar magnitude [6.8% vs. 1.8%; risk ratio 3.8 (95% CI 1.6-9.2)]. Over time, the difference in case-fatality rate for PE and DVT gradually disappeared (Table 5).

Table 3: Incidence rates (IRs) among men per 1000 person-years and 95% confidence intervals (CIs) for first deep-vein thrombosis alone (DVT) and pulmonary embolism with or without DVT (PE ± DVT) in Nord-Trøndelag County (n = 93 857) in 1995 – 2001.

		DVT alone			PE ± DVT		
Age groups (years)	Person-years	n	IR	95% CI	n	IR	95% CI
20-24	15 197	0	0	-	2	0.13	0.03-0.53
25-29	27 981	1	0.04	0.01-0.25	0	0	-
30-34	26 045	4	0.15	0.06-0.41	1	0.04	0.01-0.27
35-39	25 065	4	0.16	0.06-0.43	3	0.12	0.04-0.37
40-44	25 446	5	0.20	0.08-0.47	6	0.24	0.11-0.52
45-49	26 082	13	0.50	0.29-0.86	4	0.15	0.06-0.41
50-54	25 077	18	0.72	0.45-1.11	4	0.16	0.06-0.42
55-59	19 195	17	0.89	0.55-1.42	7	0.36	0.17-0.76
60-64	14 893	17	1.14	0.71-1.84	11	0.74	0.41-1.33
65-69	14 181	23	1.62	1.08-2.44	12	0.85	0.48-1.49
70-74	14 045	26	1.85	1.26-2.72	22	1.57	1.03-2.38
75-79	11 620	41	3.53	2.60-4.79	17	1.46	0.91-2.35
80-84	7 243	27	3.73	2.56-5.44	18	2.49	1.57-3.94
≥85	4 686	19	4.05	2.59-6.36	7	1.49	0.71-3.13
Total	256 757	215	0.84	0.73-0.96	114	0.44	0.37-0.53

Table 4: Incidence rates (IRs) among women per 1000 person-years and 95% confidence intervals (CIs) for first deep-vein thrombosis alone (DVT) and pulmonary embolism with or without DVT (PE ± DVT) in Nord-Trøndelag County (n = 93 857) in 1995 – 2001.

		DVT alone			PE ± DVT		
Age groups (years)	Person-years	n	IR	95% CI	n	IR	95% CI
20-24	14 037	3	0.21	0.07-0.66	2	0.14	0.04-0.57
25-29	25 022	2	0.08	0.02-0.32	4	0.16	0.06-0.43
30-34	23 816	6	0.25	0.11-0.56	5	0.21	0.09-0.50
35-39	23 321	9	0.39	0.20-0.74	3	0.13	0.04-0.40
40-44	24 221	4	0.17	0.06-0.44	5	0.21	0.09-0.50
45-49	24 442	20	0.82	0.53-1.27	0	0	-
50-54	23 745	17	0.72	0.44-1.15	11	0.46	0.26-0.84
55-59	18 716	17	0.91	0.56-1.46	7	0.37	0.18-0.78
60-64	15 050	14	0.93	0.55-1.57	6	0.40	0.18-0.89
65-69	15 013	17	1.13	0.70-1.82	15	1.00	0.60-1.66
70-74	15 857	23	1.45	0.96-2.18	11	0.69	0.38-1.25
75-79	14 954	44	2.94	2.19-3.95	25	1.67	1.13-2.47
80-84	11 727	45	3.84	2.87-5.14	24	2.05	1.37-3.05
≥85	9 726	46	4.73	3.54-6.31	26	2.67	1.82-3.93
Total	259 648	267	1.03	0.91-1.16	144	0.55	0.47-0.65

Table 5: Thirty-day and 1-year case-fatality rate after first VT event

		Thirty days			One year		
	Number at risk	Number of deaths	Case-fatality rate (%)	95% CI	Number of deaths	Case-fatality rate (%)	95% CI
VT	740	47	6.4	4.6-8.1	160	21.6	18.7-24.8
DVT	482	22	4.6	2.9-6.8	101	21.0	17.4-24.9
PE	258	25	9.7	6.1-13.3	59	22.9	17.9-28.5
Idiopathic[§]	373	15	4.0	2.3-6.5	54	14.5	11.3-18.5
Secondary[¶]	236	7	3.0	1.2-6.0	23	9.7	6.6-14.3
Cancer[#]	131	25	19.1	12.3-25.9	83	63.4	55.6-71.9
Non-cancer							
VT	609	22	3.6	2.3-5.4	77	12.6	10.1-15.5
DVT	389	7	1.8	0.7-3.7	43	11.1	8.1-14.6
PE	220	15	6.8	3.9-11.0	34	15.5	10.9-20.9

VT, venous thrombosis; DVT, deep-vein thrombosis; PE, pulmonary embolism;.
[§]Idiopathic VT.
[¶]Secondary non-cancer VT.
[#]VT secondary to cancer.

The 1-year case-fatality rate was 21.6% (n = 160; 95% CI: 18.7-25.8) in all the cases, it was 12.6% (n = 77; 95% CI: 10.1-15.5) in patients with thrombosis without cancer, as compared to 63.4% (n = 83; 95% CI: 54.5-71.8) in thrombosis patients with cancer. The Kaplan-Meyer overall survival plot showed poor survival in cases with cancer (Fig. 2). The survival for patients with secondary non-cancer VT and idiopathic VT was higher than for patients with VT secondary to cancer. Between patients with secondary non-cancer VT and idiopathic VT, the difference in observed survival was small.

In comparison to the general population and adjusted for sex and age, the hazard ratios for death for the whole follow-up period after VT were two times higher in patients with secondary non-cancer VT, 2.5 times higher for those with idiopathic VT and 13 times higher among VT patients with cancer (Table 6). We subdivided the follow-up after VT into three periods: 0-0.5 years after the event, 0.5-3 years after the event, and 3 years or more after the event. In patients with secondary non-cancer VT, there was no increased mortality beyond 6 months after the event in comparison to the general population. Among patients with idiopathic VT, the hazard ratio declined to 1.2 after 3 years as compared to the general population. In VT patients with cancer, the hazard ratio of death declined from more than thirtyfold during the first 6 months to less than 3-fold 3 years after the event as compared to the general population (Table 6). The mortality rate was slightly lower in women than in men [age-adjusted hazard ratio 0.8 (95% CI: 0.7-1.1)].

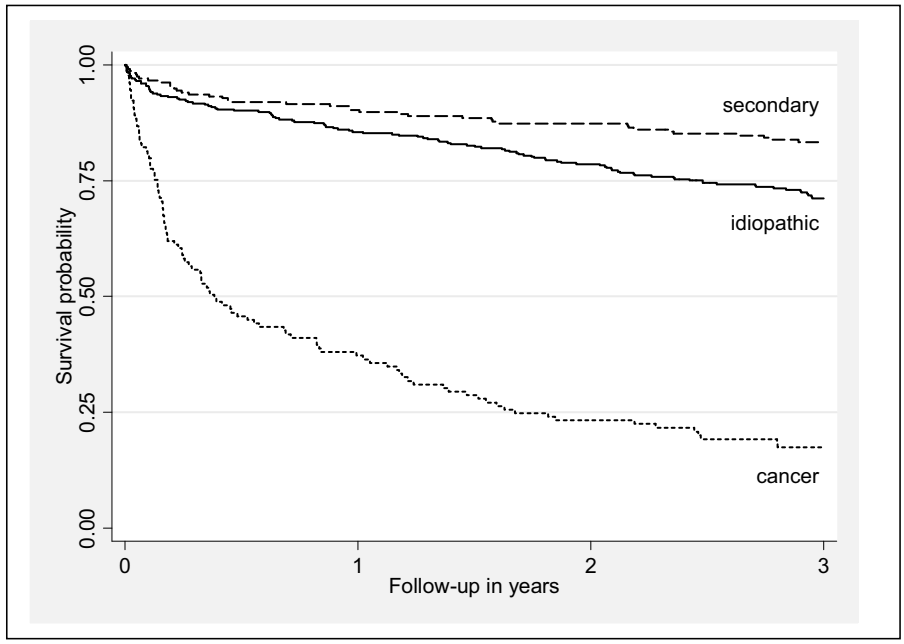

Figure 2. Kaplan-Meyer survival probability after first venous thrombosis (VT) in the risk groups of secondary non-cancer VT (secondary), idiopathic VT (idiopathic) and VT secondary to cancer (cancer), respectively

Table 6: Hazard ratio of death after first venous thrombosis (VT) event in different risk groups compared to the general population according to different follow-up periods.

		Hazard ratio (95% CI)*			
			Periods of follow-up after VT		
	Number at risk	Total follow-up[#]	0-0.49 year	0.50-2.99 years	≥3 years
Total population	92 804	1	1	1	1
Idiopathic[†]	373	2.57 (2.17-3.04)	4.36 (3.12-6.08)	1.83 (1.44-2.32)	1.24 (0.87-1.75)
Secondary[‡]	236	1.97 (1.52-2.57)	4.85 (3.07-7.66)	1.05 (0.68-1.63)	1.09 (0.68-1.75)
Cancer[¶]	131	12.73 (10.59-15.29)	33.78 (26.41-43.21)	7.29 (5.25-10.13)	2.48 (1.24-4.95)

*Adjusted for sex and age.
[†]Idiopathic VT.
[‡]Secondary non-cancer VT.
[¶]VT secondary to cancer.
[#]From entry to end of follow-up. VT was entered as time dependent variable. Proportional hazard not met.

Discussion

We studied the complete population of Nord-Trøndelag County for 6.5 years, and found that the incidence rate of a first VT event in people aged 20 years or more was 1.43 per 1000 person-years. The risk of dying was highest shortly after the VT event. During the first year after the event, the risk of dying in the patients gradually approached that in the general population.

Our observed incidence rate of VT is similar to rates for first events in Brest, France [8], Göteborg, Sweden [7] and two studies in the USA: Olmsted County, Minnesota [9] and the LITE study [5].

The 30-day case-fatality rate of 6.4% and 1-year case-fatality rate of 21.6% in our study are similar to those in other cohort studies that excluded patients with autopsy-verified thrombosis [4,5,23]. In contrast, studies including autopsies reported a 30-day case-fatality rate of 28% [15] and a 1-year case-fatality rate close to 40% [15,21].

The high case-fatality rate in patients with a first VT event secondary to cancer is similar to that in other studies [4,5,15,23]. The increased mortality rate is most likely related mainly to the cancer itself. The follow-up study of Sørensen et al. [29] suggests that occurrence of thrombosis in cancer patients is associated with substantially increased mortality. It is unclear whether this is causally related to the thrombosis, or whether the thrombosis is a marker of an aggressive malignancy.

The strengths of our study are the high quality of the outcome data, the large population at risk, and the population-based design, with individual data from the HUNT2 study and the National death register on age, sex, death and emigration.

In comparison to existing studies, our advances are a complete population, a long follow-up time, exact person-time calculations, a complete case-finding procedure, and individually validated VT diagnoses.

However, we may have underestimated the incidence rate, for several reasons. We had data on emigration from Norway, but not on migration from the county to other counties within the country. Census data (http://www.ssb.no/statistikkbanken/) showed that the number of migrants to other parts of the country is about 2,500 each year from Nord-Trøndelag. Age-specific data showed that these persons are young people, perhaps students, who often move back within a few years. Nevertheless, this may have led to an overestimation of the person-time. We performed a sensitivity analysis to assess the potential impact on the incidence estimate. The amount of excess person-years contributed by migration within the country was estimated to be 41,000. After subtraction of the excess person-years in relevant 10-year age bands, the estimated overall incidence rate increased only slightly from 1.43 to 1.52 per 1000 person-years.

The presence of persons in the study population with an unknown previous thrombosis, and therefore not at risk for a first thrombosis, may also have led to underestimation of the incidence rate. However, this would lead to only a small change in the overall number of person-years at risk, and thus would have a negligible influence on the incidence rate estimate.

In addition to the 740 certain cases of VT identified during follow-up, we also identified 182 otherwise eligible cases among the 258 possible VT events (no objective diagnostic

procedures were performed, or the results were indeterminate) that were not included in the incidence estimate. If these cases had been definite cases and had been included, the estimated standardized incidence rate would have been 1.78 per 1000 person-years instead of 1.43 per 1000 person-years.
Cases diagnosed post mortem were not included in this study. The number of cases diagnosed post mortem will vary between studies, depending on differences in autopsy rates, and this makes it difficult to compare incidence rates between studies. The autopsy rate is low in Norway, and if they had been included, we would still have underestimated the incidence rate, because of an unknown number of undiagnosed events.
VT secondary to acquired risk factors was as common as idiopathic thrombosis in our study. Surgery and cancer were the most common risk factors, and improved prophylaxis in these patient groups might lower the incidence of VT.
In conclusion, this study provides an estimate of the incidence and mortality of first VT events in an unselected general population. The incidence increased nearly exponentially with age, and the proportion of VT events secondary to acquired risk factors was 50%. In comparison to the general population, the mortality rate was highest during the first months after the VT event, after which it gradually approached the rate in the general population.

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Appendix
Discharge codes used to identify potential cases of DVT and PE before the validation process were ICD-9 codes 415.x, 451.x, 452, 453.x, 325, 362.3, 433, 557.0, 634-638 (with decimals 6 and 7), 639.6, 639.8, 639.9, 671.x, 673.x, 674, and 997.2, and ICD-10 codes I26.x, I80.x, I81, I82.x, I63.6, I67.6, K55, H34.8, O08.x, O22.x, O87.x, and O88.x.

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