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ORIGINAL ARTICLE

Recurrence and mortality after first venous thromboembolism in a large population-based cohort

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Essentials

- Reports on recurrence and mortality after a first venous thromboembolism (VTE) vary considerably.
- We describe rates of recurrence and mortality in patients with a first VTE from the Tromsø study.
- The overall recurrence rate was 3.9 per 100 person-years, but this varied widely with time.
- Despite advances in VTE management, the rates of adverse events are still fairly high.

Summary. *Background:* Previous reports on recurrence and mortality rates after a first episode of venous thromboembolism (VTE) vary considerably. Advances in the management and treatment of VTE during the last 15 years may have influenced the rates of clinical outcomes. *Aim:* To estimate the rates of recurrence and mortality after a first VTE in patients recruited from a large population-based cohort. *Method:* From the Tromsø study, patients (n = 710) with a first, symptomatic, objectively confirmed VTE were included and followed in the period 1994–2012. Recurrent episodes of VTE were identified from multiple sources and carefully validated by review of medical records. Incidence rates and cumulative incidence rates with 95% confidence intervals (CIs) of VTE recurrence and mortality were calculated. *Results:* The mean age of the patients was 68 years (range 28–102 years), and 166 (23.4%) had cancer at the time of first VTE. There were 114 VTE recurrences and 333 deaths during a median study period of 7.7 years (range 0.04–18.2 years). The risk of recurrence was highest during the first year. The overall 1-year recurrence rate was 7.8 (95% CI 5.8–10.6) per 100 person-years (PY), whereas the recurrence rate in the remaining follow-up period (1–18 years) was 3.0 (95% CI 2.4–3.8) per 100 PY. The overall 1-year all-cause mortality rate was 29.9 (95% CI 25.7–34.8) per 100 PY, and in those without cancer the corresponding rate was 23.6 (95% CI 17.8–31.3) per 100 PY. *Conclusion:* Despite advances in VTE management, the rates of adverse events remained fairly high, particularly in the first year following a first VTE.

Keywords: cancer; epidemiology; mortality; recurrence; venous thromboembolism.

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Introduction

Venous thromboembolism (VTE) is a common term for deep vein thrombosis (DVT) and pulmonary embolism (PE). The annual incidence of VTE is approximately 1–3 per 1000 in the adult population of high-income countries [1–4], and the risk increases exponentially with age [5]. With high rates of recurrence and mortality, as well as increased long-term morbidity and functional disability, VTE remains a major public health concern with a substantial disease burden [6].

Previously reported rates of recurrence and survival after a first VTE vary widely, ranging from 0.6% to 5% at 30 days, and from 25% to 40% at 10 years, for VTE recurrence [3,7–16], and from 77% to 97% at 1 week, and from 61% to 75% at 8 years, for survival [3,7,16–18]. The differences in the reported rates may, to some extent, be ascribed to differences in study design (e.g. clinical trials, cohorts or registry databases with limited case validation), clinical setting (hospital or community setting), and the time period over in which the study was conducted. Advances in diagnostics, management and treatment of VTE in recent years may have influenced the rates of adverse outcomes after VTE. The introduction of low molecular weight heparins for the treatment of acute VTE in the early 1990s [19] has reduced the length of

hospital stays after VTE, and a larger proportion of the VTE cases are currently treated as outpatients [20,21]. Furthermore, increased awareness of VTE risk and the use of thromboprophylaxis in high-risk situations may have impacted on recurrence and mortality rates. Finally, the more widespread use of spiral computed tomography (CT) to diagnose PE, and the concomitant increased detection of subsegmental PE [22], may have influenced the overall outcome rates after a first VTE.

VTE is a multifactorial disease that occurs frequently in association with cancer and other comorbidities. A high mortality rate resulting from other conditions will result in an overestimation of the cumulative incidence of recurrence in patients with a first VTE, as death is a competing event [23,24]. Few studies have assessed and compared the cumulative incidence of recurrence in the presence of competing risk of death in subgroups of patients with a first VTE [25,26]. Moreover, many of the previous studies were carried out several decades ago [7,13,17], were restricted to either the hospital or community setting [7,15,27], or included their patients after completion of anticoagulant treatment (i.e. 3–12 months after the first event) [7,27,28]. We therefore aimed to estimate the cumulative incidence of recurrence and mortality after a first VTE by using cases derived from a general population cohort including both the hospital and outpatient setting, during the period 1994–2012.

Methods

Study population

Patients with a first lifetime VTE were recruited from the fourth survey of the Tromsø Study, a population-based cohort study in which 26 855 subjects age 25–97 years were enrolled in 1994–1995 and followed up to December 2012, as previously described in detail [29]. The study was approved by the regional committee for research ethics, and all participants gave their informed, written consent to participate. In total, 710 incident symptomatic VTE cases were included in the study. Recurrent VTE events and all-cause mortality among the incident cases were recorded until the end of follow-up on 31 December 2012.

Identification and validation of VTE

All first lifetime episodes of VTE were identified by searching the hospital discharge registry, the autopsy registry and the radiology procedure registry at the University Hospital of North Norway, from the date of enrolment in the Tromsø Study (1994–1995) to 31 December 2012. The University Hospital of North Norway is the only hospital in the region, and all hospital care and relevant diagnostic radiology for VTE in the Tromsø community is provided exclusively by this hospital. We used a broad search strategy, and the relevant discharge codes were ICD-9 codes 325, 415.1, 451, 452, 453, 671.3, 671.4 and 671.9 for the period 1994–1998, and ICD-10 codes I26, I67.6, I80, I81, I82, O22.3, O22.5, O87.1 and O87.3 for the period 1999–2012. The hospital discharge registry included both outpatient clinic visits and hospitalizations. An additional search of the computerized index of autopsy diagnoses was conducted, and cases diagnosed with VTE, either as a cause of death or as a significant condition, were identified. We also searched the radiology database in order to identify potential cases of symptomatic objectively confirmed VTE that may have been missed because of coding errors in the hospital discharge registry. Trained personnel systematically reviewed all relevant diagnostic procedures performed at the Department of Radiology to diagnose VTE during the 18-year period, and cases with objectively confirmed VTE were identified.

The medical records for each potential VTE case derived from the hospital discharge registry, the autopsy registry and the radiology procedure registry were reviewed by trained personnel for case validation. For subjects derived from the hospital discharge registry and the radiology procedure registry, an episode of VTE was verified and recorded as a validated outcome when all four of the following criteria were fulfilled: (i) signs and symptoms consistent with DVT or PE were present; (ii) objectively confirmed by diagnostic procedures (compression ultrasonography, venography, spiral CT, perfusion–ventilation scan, pulmonary angiography, or autopsy); (iii) the medical record indicated that a physician had made a diagnosis of DVT or PE; and (iv) the patient received treatment with anticoagulants (heparin, warfarin, or a similar agent), thrombolytics, or vascular surgery, unless contraindications were specified. For subjects derived from the autopsy registry, a VTE event was recorded as an outcome when the autopsy record (death certificate) indicated VTE as the cause of death or as a significant condition contributing to death.

A VTE event was classified as cancer-related, provoked, or unprovoked, based on the presence of cancer or other provoking factors at the time of VTE diagnosis. The presence of cancer was defined as overt cancer at the time of VTE diagnosis (or, in some cases, if cancer was diagnosed on the same day as the VTE). Non-melanoma skin cancer (ICD-10 code C44) was not registered as cancer. VTEs occurring in patients with active cancer were classified as cancer-related regardless of other risk factors. In patients without cancer, a VTE occurring in the presence of one or more provoking factors was defined as provoked. The following were regarded as provoking factors: recent hospitalization, surgery, or trauma (within 8 weeks before the event), an acute medical condition (acute myocardial infarction, acute ischemic stroke, or acute infections), immobilization (bed rest for > 3 days, wheelchair use, or

long-distance travel for ≥ 4 h within the last 14 days), or another factor specifically described as provoking by a physician in the medical record (e.g. intravascular catheter). VTEs occurring in patients without cancer or any provoking factor were classified as unprovoked.

Outcomes

We recorded all VTE recurrences and deaths among the study participants during follow-up. Recurrent VTEs were identified and validated with the same approaches and criteria as used for first VTE described above. Information on deaths was collected from the Norwegian Population Registry by use of the unique national person identification number.

Statistical analyses

Statistical analyses were carried out with STATA version 14.0 (Stata Corporation, College Station, TX, USA). Descriptive statistics for baseline data were reported as percentages or means (with standard deviations), as appropriate. For analyses of recurrence, the patients (n = 710) were followed from the date of their first VTE until the date of VTE recurrence, date of migration, date of death, or study end (31 December 2012), whichever came first. Crude recurrence rates were calculated by dividing the number of recurrent events by the total person-years (PY) at risk, and expressed per 100 PY. Moreover, recurrence rates were calculated for the various subtypes of VTE (cancer-related, unprovoked, and provoked) in different time intervals (0–6 months, 6 months to 1 year, 1–5 years, 5–10 years, and > 10 years) after the first event. 1-Kaplan–Meier estimates with 95% confidence intervals (CIs) were used to report the cumulative incidence of recurrence over time in men and women, and according to subtype and location (DVT and PE) of the index VTE. Cox proportional hazards regression was used to calculate the hazard ratios (HRs) of recurrence and mortality in men and women and according to the classification (cancer-related, provoked, and unprovoked) and localization (DVT and PE) of the first VTE adjusted for age and sex.

For analyses of mortality, subjects were followed from the date of the first VTE until the date of death or study end (31 December 2012). Subjects who died on the same day as the VTE (n = 18) were given 1 day of follow-up in the analyses. Crude mortality rates were calculated as the number of deaths divided by the total PY at risk, and expressed per 100 PY. Similarly, we estimated mortality rates according to type and localization of the first VTE in different time intervals, and Kaplan–Meier curves were used to visualize survival over time for men and women and according to subtypes of VTE.

The cumulative incidence of VTE recurrence is dependent on both the risk of recurrence and the risk of dying, and, consequently, recurrence risks are overestimated when the mortality rate is high. We therefore estimated the cumulative incidence of recurrence in the presence of competing risk of death by using the stcrreg and stcurve cif commands in STATA.

Results

Patient characteristics

The clinical characteristics assessed at the time of incident (n = 710) and recurrent (n = 114) VTE events are summarized in Table 1. The mean age at the time of the first

Table 1 Baseline and clinical characteristics of incident (n = 710) and recurrent venous thromboembolism (VTE) cases (n = 114); the Tromsø Study 1994–2012

Variables	Incident (n = 710)	Recurrent (n = 114)
Age (years), mean ± SD	68.7 ± 13.5	70.6 ± 12.0
Gender (male), no. (%)	329 (46.3)	61 (53.5)
PE, no. (%)	295 (41.5)	46 (40.3)
DVT, no. (%)	415 (58.4)	68 (59.6)
Proximal leg DVT, no. (%)	314 (44.2)	58 (50.8)
Calf vein DVT, no. (%)	131 (18.4)	19 (16.6)
VTE at other site, no. (%)	32 (4.5)	4 (3.5)
Unprovoked, no. (%)	295 (41.5)	55 (48.2)
Cancer-related, no. (%)	166 (23.3)	28 (24.5)
Treatment duration with AC (months), no. (%)		
0–3	247 (34.7)	29 (25.4)
3–6	229 (32.2)	13 (11.4)
6–12	137 (19.2)	14 (12.2)
> 12	65 (9.1)	53 (46.5)
Provoking factors, no. (%)		
Acute medical condition *,†	102 (14.3)	13 (11.4)
Surgery†	107 (15)	12 (10.5)
Trauma†	56 (7.9)	3 (2.6)
Immobilization	135 (18.9)	20 (17.4)
Bed rest for ≥ 3 days	47 (6.6)	8 (7.0)
Long-haul travel‡	6 (0.8)	3 (2.6)
Other immobilization	82 (11.5)	9 (7.8)
Other provoking factor	36 (5.0)	5 (4.4)
One provoking factor	182 (25.6)	24 (21.1)
More than one provoking factor	99 (13.9)	11 (9.6)
Clinical risk factors, no. (%)		
Recent hospitalization†	288 (40.5)	45 (6.3)
Nursing home	39 (5.5)	8 (7)
Estrogen usage §	40 (5.6)	2 (1.7)
Heredity¶	20 (2.8)	3 (2.6)
Obesity	116 (16.3)	19 (16.6)
Comorbidity**	157 (22.1)	24 (21.0)
Pregnancy/puerperal period	3 (0.4)	–

AC, anticoagulant; DVT, deep vein thrombosis; PE, pulmonary embolism; SD, standard deviation. *Acute myocardial infarction, ischemic stroke, or major infectious disease. †Within 8 weeks prior to the VTE event. ‡Travel exceeding 4 h within the last 14 days. §Hormone replacement therapy/oral contraceptives. ¶Heredity: family history of VTE in first-degree relative before the age of 60 years. **Comorbidity within the previous year (myocardial infarction, ischemic stroke, heart failure, inflammatory bowel disease, chronic infections, chronic obstructive pulmonary disease, or myeloproliferative disorders).

VTE was 68.7 ± 13.5 years (range 28–102 years), and the proportion of men was 46.3%. Furthermore, 42% of the incident VTE events were classified as unprovoked, 23% as cancer-related, and 35% as being provoked by a factor other than cancer. The mean age at recurrence was 70.6 years (range 36–97 years), and the proportion of men was 46.5%. Among the recurrences, 48.2% were classified as unprovoked, 24.5% as cancer-related, and 27.3% as being provoked by factors other than cancer.

Recurrent VTE

Of the 710 incident VTE cases, 114 patients had a recurrent VTE event (PE in 46 and DVT in 68) during a median of 2.7 years of follow-up (range 1 day to 18.1 years). The overall recurrence rate was 3.9 (95% CI 3.3–4.7) per 100 PY; 4.5 (95% CI 3.5–5.8) in men, and 3.4 (95% CI 2.6–4.4) in women. The incidence rates of recurrence per 100 PY were 8.5 (95% CI 5.5–13.2) for cancer-related VTE, 3.4 (95% CI 2.5–4.7) for provoked VTE, and 3.6 (95% CI 2.7–4.6) for unprovoked VTE.

The recurrence rate varied widely during follow-up, as it was highest in the beginning and declined in later years. The overall recurrence rates per 100 PY were 9.2 (95% CI 6.2–13.3) in the first 6 months, 6.3 (95% CI 3.8–10.3) in the period 6 months to 1 year, 3.5 (95% CI 2.6–4.6) in the period 1–5 years and 2.3 (95% CI 1.5–3.7) in the 5–10 years after the index event (Table 2).

The cumulative incidence rates of overall VTE recurrence were 1.7% (95% CI 1.0–3.1) at 1 month, 4.3% (95% CI 3.0–6.2) at 6 months, 7.2% (95% CI 5.4–9.7) at 1 year, 18.8% (95% CI 15–22) at 5 years and 28.3% (95% CI 23–33) at 10 years of follow-up (Table S1). The 10-year cumulative incidence rates of recurrence were 35.4% in men and 22.0% in women (Fig. 1A), which corresponded to a 1.3-fold (95% CI 0.96–2.03) higher risk of recurrence in men than in women.

The cumulative incidence of VTE recurrence according to classification of the initial event is shown in Fig. 2A. The 5-year cumulative incidence rates were 17.9% in unprovoked, 16.7% in provoked and 26.4% in cancer-related VTE, respectively (Fig. 2A; Table S1). When competing risk of death was taken into account, the corresponding figures were 16.1% in unprovoked, 14.4% in provoked and 11.4% in cancer-related incident VTE (Fig. 2B).

The recurrence risk was higher in patients with initial DVT than in patients with PE throughout the 10-year period (Fig. 1B). The HR of recurrence was 1.4-fold higher (HR 1.45, 95% CI 0.96–2.18) in those with DVT than in those with PE. Furthermore, patients with a first PE were 2.4-fold more likely to develop a second PE rather than a DVT, and vice versa (Table 3). Among the 34 patients with a first PE, 24 (70.6%) had recurrent PE and 10 (29.4%) had recurrent DVT. Correspondingly, among the 80 patients with a first DVT, 22 (27.5%) had recurrent PE and 58 (72.5%) had recurrent DVT. Likewise, patients with a first unprovoked VTE were more likely to have their second event unprovoked (Table 4). Among those with a first unprovoked VTE, 66.7% experienced a second unprovoked event, 20.4% had a provoked VT, and 12.9% had a cancer-related VTE as the recurrent episode. Those with a first provoked VTE were just as likely to have a second provoked or unprovoked VTE (47.5% versus 45%, respectively), and 7.5% had a cancer-related VTE as the recurrent episode (Table 4).

All-cause mortality

During follow-up, 333 of the 710 VTE patients died. The overall mortality rate during a median of 3.4 years of follow-up (range 1 day to 18 years) was 9.7 per 100 PY (95% CI 8.7–10.8). The crude mortality rate was higher in women (11.0 per 100 PY, 95% CI 9.5–12.7) than in men (8.3 per 100 PY, 95% CI 7.1–10.0); however, the CIs overlapped. Correspondingly, the cumulative probability of survival beyond 10 years was higher in men (48.4%, 95% CI 41.5–55.0) than in women (41.1%, 95% CI 35.1–47.1) (Fig. 3A). The higher mortality rate among women was explained by their higher age at the

Table 2 Incidence rates (IRs) with 95% confidence intervals (CIs) of venous thromboembolism (VTE) recurrence (per 100 person-years) in different time intervals after VTE and according to classification of the index VTE; the Tromsø Study 1994–2012

Time	Overall VTE *n* IR (95% CI)	Cancer-related VTE *n* IR (95% CI)	Provoked VTE* *n* IR (95% CI)	Unprovoked VTE *n* IR (95% CI)
0–6 months	27 9.2 (6.2–13.3)	9 17.8 (9.2–34.3)	11 10.4 (5.7–18.8)	7 5.0 (2.4–10.6)
6 months to 1 year	16 6.3 (3.8–10.3)	6 18.1 (8.1–40.3)	5 5.4 (2.2–13.0)	5 3.9 (1.6–9.4)
1–5 years	47 3.5 (2.6–4.6)	4 3.5 (1.3–9.5)	14 2.6 (1.5–4.4)	29 4.1 (2.8–5.8)
5–10 years	18 2.3 (1.5–3.7)	–	8 2.4 (1.2–4.8)	10 2.5 (1.3–4.7)
After 10 years	6 2.4 (1.0–5.3)	1 20.5 (2.8–145.9)	2 1.8 (0.4–7.5)	3 2.1 (0.6–6.7)

*Without cancer.

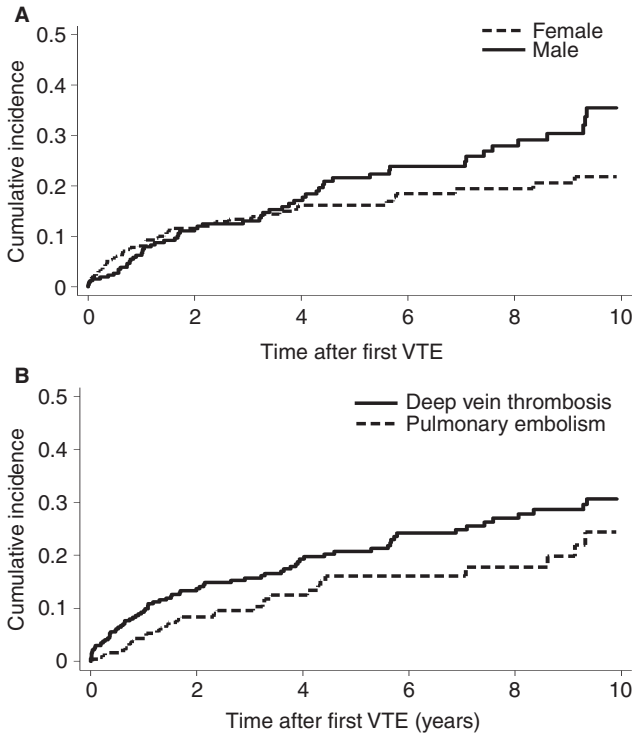

Fig 1. Cumulative incidence of venous thromboembolism (VTE) recurrence. (A) 1-Kaplan–Meier curves for men and women. (B) 1-Kaplan–Meier curves according to initial deep vein thrombosis and pulmonary embolism.

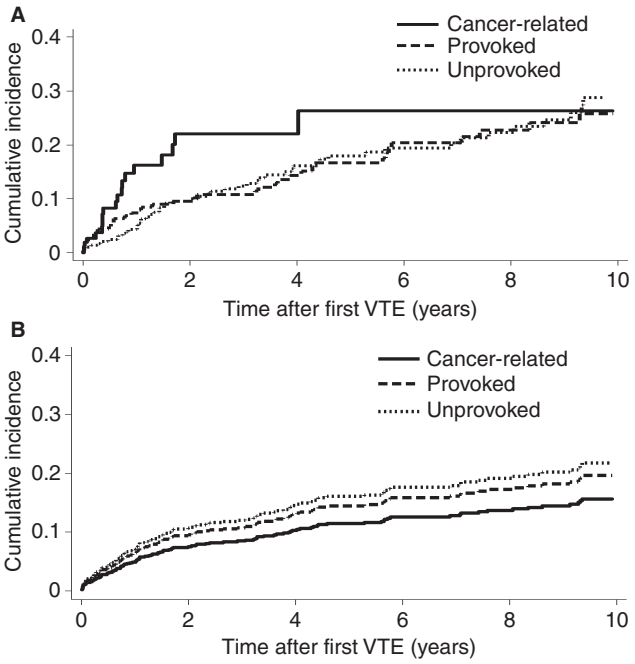

Fig 2. Cumulative incidence of venous thromboembolism (VTE) recurrence according to classification of the index event. (A) 1-Kaplan–Meier curves. (B) Cumulative incidence after taking competing risk of death into account.

Table 3 Recurrence sites (%) according to site of the index venous thromboembolism

	Second event		
First event	Pulmonary embolism	Deep vein thrombosis	Total
Pulmonary embolism	24 (70.6)	10 (29.4)	34
Deep vein thrombosis	22 (27.5)	58 (72.5)	80
Total	46 (40.3)	68 (59.6)	114

Table 4 Classification of recurrences (%) according to the classification of the index venous thromboembolism

	Second event			
First event	Unprovoked	Provoked*	Cancer-related	Total
Unprovoked	36 (66.7)	11 (20.4)	7 (12.9)	54
Provoked*	18 (45.0)	19 (47.5)	3 (7.5)	40
Cancer-related	1 (5.0)	1 (5.0)	18 (90.0)	20
Total	55 (48.2)	31 (27.2)	28 (24.6)	114

*Without cancer.

index date, as the HR of death for men versus women changed from 0.78 (95% CI 0.63–0.97) to 0.96 (95% CI 0.77–1.21) after adjustment for age.

The mortality rate was highest in the first 6 months after the VTE event, and declined rapidly thereafter (Table 5). The 1-year mortality rate in patients with cancer-related VTE was 114.4 (95% CI 94.0–139.3) per 100 PY.

The cumulative incidence of all-cause mortality after VTE is shown in Table S2. The 10-year cumulative incidence of mortality was highest among those with cancer-related VTE (88.3%), and lowest among those with unprovoked VTE (41.5%) (Fig. 3B).

Discussion

The present study was conducted to determine recurrence and mortality rates after a first event of VTE in a cohort of patients recruited from the general population in the period 1994–2012, including both the community and hospital setting. The overall recurrence rate was 3.9 per 100 PY, but varied widely with time, from 9.2 per 100 PY in the first 6 months to 2.3 per 100 PY in the 5–10 years after the first VTE event. The overall 10-year cumulative incidence rates of recurrence were 35.4% in men and 22.0% in women. The cumulative incidence of recurrence was high among cancer patients, particularly in the first year (16.3%). However, after competing risk of death was taken into account, the cumulative incidence rates of recurrence were 4.9% at 1 year and 11.4% at 5 years in cancer patients, whereas the corresponding rates in non-cancer patients were 6.3% and 14.4%. The 30-day and 1-year cumulative all-cause mortality rates after VTE were 19.4% and 62.0% in cancer patients, and 9.0% and 16.6% in cancer-free patients, respectively.

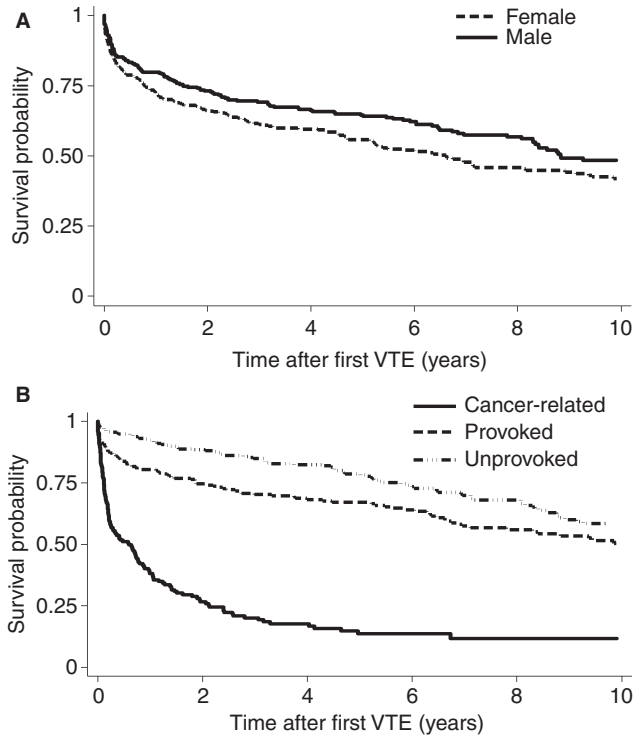

Fig 3. Survival probability after venous thromboembolism (VTE). (A) Kaplan–Meier curves in men and women. and (B) VTE by classification of the initial event.

Advances in diagnostic tools and the management and treatment of VTE in recent years may have influenced the outcome rates after a first VTE. Few studies have recently described this in a setting that covers provoked and unprovoked first events derived from both the hospital and community setting with long-term follow-up starting from the date of first VTE. Our recurrence rates were only marginally lower than those reported by Heit *et al.* [13], who investigated recurrence among 1791 patients with a first VTE in the period 1960–1999. They reported overall cumulative incidence rates of recurrence of 12.9% at 1 year and 30.4% at 10 years, whereas the corresponding numbers in our study were 7.2% and 28.3%. In the Worcester study [28], conducted in the period 1999–2003, the 1-year cumulative incidence of recurrence was 10.9%, but they did not report on long-term follow-up. Improved treatment strategies may, to some extent, explain the lower 1-year cumulative recurrence risk observed in our study than in the previous studies. Nevertheless, in the long term, our cumulative incidence of recurrence was similar to that in previous studies, suggesting a catch-up effect after the initial period [15,30]. Thus, despite advances in diagnosis and treatment in recent years, the rates of recurrence after VTE were still high, particularly in the long term.

The recurrence rate was highest during the initial 6 months after the VTE in all subgroups, despite the fact that most patients received anticoagulant therapy in this period. This highlights the importance of including patients at the time of the event, particularly for descriptive epidemiologic purposes, as studies that start their follow-up after the withdrawal of anticoagulants will lose a significant amount of cases that occur in the initial phase.

In agreement with previous studies [25,26], the 5-year cumulative risk of recurrence was highest among cancer patients. The mortality rate is high among cancer patients, and, in the presence of competing risk of death, the cumulative incidence of recurrence is dependent on both the risk of recurrence and the risk of dying [23,24,31]. Therefore, when competing risk of death was taken into account, the estimated 5-year cumulative risk of recurrence changed from 26.4% to 11.4% in cancer patients, and the risk of recurrence in cancer patients was actually lower than in those with unprovoked and provoked VTE (16.1% and 14.4%, respectively).

In our study, patients with a first DVT had a 1.4-fold higher risk of recurrence than those with a first PE. This finding is in agreement with a Canadian study of 646 patients with first unprovoked VTE showing that subjects with DVT had a two-fold higher risk of recurrence than

Table 5 All-cause mortality rates (MRs) per 100 person-years in different time intervals after venous thromboembolism (VTE) and according to classification of the index event; the Tromsø Study 1994–2012

Time	Overall VTE *n* MR (95% CI)	Cancer-related VTE *n* MR (95% CI)	Provoked VTE* *n* MR (95% CI)	Unprovoked VTE *n* MR (95% CI)
0–6 months	134 44.7 (37.7–52.9)	79 153.3 (122.9–191.1)	40 37.2 (27.3–50.7)	15 10.6 (6.4–17.6)
6 months to 1 year	35 13.3 (9.5–18.5)	20 57.1 (36.8–88.5)	8 8.3 (4.1–16.7)	7 5.2 (2.4–10.9)
1–5 years	95 6.2 (5.1–7.6)	33 28.9 (20.5–40.6)	28 4.8 (3.3–6.9)	34 4.0 (2.9–5.7)
5–10 years	56 5.8 (4.5–7.6)	1 2.6 (0.3–18.8)	23 5.8 (3.8–8.7)	32 6.0 (4.2–8.5)
After 10 years	13 3.5 (2.0–6.1)	1 10.7 (1.5–76.0)	6 4.1 (1.8–9.1)	6 2.8 (1.2–6.4)

CI, confidence interval. *Without cancer.

those with PE [32]. Likewise, the study by Prandoni *et al.* [18] found that DVTs were 1.4-fold more likely to recur than PEs. Potential explanations for this phenomenon may be more efficient clot resolution in the lungs, owing to high fibrinolytic activity [33], in contrast to venous valve damage and development of the post-thrombotic syndrome, which frequently occurs among patients with DVT [7]. Moreover, the introduction of CT to diagnose PE may have led to increased detection of subsegmental PEs, which have a better prognosis with regard to recurrence [22].

In accordance with previous studies [18,34,35], the type of the first VTE was a predictor for the type of recurrence, as patients with a first PE were 2.4-fold more likely to have a second PE rather than a DVT. Moreover, we showed that those with a first unprovoked VTE were more likely to have a second unprovoked VTE, whereas those with a first provoked VTE were just as likely to have a provoked or unprovoked VTE as their second event. The latter may be explained by an altered baseline risk following the first provoked VTE, e.g. residual vein thrombosis [36,37] or other pathophysiologic changes in the veins caused by the first VTE increasing the chance of having a recurrent thrombosis, even in the absence of provoking factors.

Most previous studies have reported a two-fold to four-fold higher recurrence rate among men than among women [27,34,38]. In our study, we confirmed this trend, but the relative risk of recurrence was only 30% higher in men than in women, and the difference was not statistically significant. As the source population for our VTE cases was restricted to subjects aged $\geq$ 25 years, our study population did not contain the very young women with a first VTE often related to oral contraceptives or pregnancy. Generally, the young women with hormone-related VTE have a low recurrence risk [39], and, as a result, the risk difference between men and women will be higher in a VTE population that contains these women. The cumulative incidence curves for recurrence in men and women started to separate 3 years after the initial event in our study, which may partly explain why higher relative risk differences in men versus women are reported in studies with a later start of follow-up (after withdrawal of anticoagulants).

The 1-year mortality rates after VTE remained high (24% in all VTE patients and 62% in cancer-related VTE patients), and were remarkably similar to those reported in a previous Norwegian study of 740 VTE patients recruited in the period 1995–2001 [40]. We observed a higher survival rate among men in our crude analyses, but this was explained by age differences among men and women at the time of the index event. Subjects with provoked VTE had poorer survival than those with unprovoked VTE, which can probably be explained by a higher age and more comorbidities among those with provoked VTE.

The strengths of our study include the unselected VTE patients recruited from the general population covering both the community and the hospital setting, thoroughly identified and individually validated first and recurrent events, the relatively long follow-up, and data collected from a recent calendar period. Patients were treated according to standard practice. As our study center is the only diagnostic and treatment facility for all patients in the area, few cases were lost to follow-up, and we therefore believe that our observations reflect the true clinical course of VTE. Moreover, few previous studies have compared the cumulative incidence of recurrence among subgroups in the presence of competing risk of death. Unfortunately, the study population was too small to for trends in recurrence and mortality over time to be investigated, and we did not have sufficient information on causes of death. Moreover, the VTE population was only representative for the population aged $\geq$ 28 years. However, as the incidence increased sharply with age, our VTE population covered the vast majority of the total VTEs in the general population. Unfortunately, we did not have detailed information on the duration of anticoagulant treatment after VTE. However, adjustment for the planned duration, which, in most cases, is expected to reflect the actual duration, did not have a major impact on the difference in recurrence risk between unprovoked and provoked VTE.

Despite advances in VTE management in recent years, the rates of adverse events remained high, especially in the first year following a VTE. VTE recurs frequently, and this trend continues for at least 10 years and possibly longer after the incident event. In order to reduce the disease burden associated with VTE, future studies should focus on the development of risk prediction models with high precision, in order to identify high-risk individuals with a favorable benefit-to-harm ratio for anticoagulant treatment.

Addendum

N. Arshad analyzed data and wrote the manuscript. E. Bjøri interpreted data and revised the manuscript. K. Hindberg provided statistical support, interpreted data, and revised the content. T. Isaksen collected data and revised the manuscript. J.-B. Hansen was responsible for the concept and design of the study, data collection and interpretation, and revision of the manuscript. S. K. Brækkan was responsible for the concept and design of the study, data collection and interpretation, and writing of the manuscript.

Disclosure of Conflict of Interests

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Cumulative incidence of venous thromboembolism (VTE) recurrence according to classification of the index VTE. The Tromsø Study 1994–2012.

Table S2. Cumulative incidence of all-cause mortality according to time since venous thromboembolism and classification of the index event. The Tromsø Study 1994–2012.

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Supplementary Tables

Supplementary table 1 Cumulative incidence of VTE recurrence according to classification of the index VTE. The Tromsø Study 1994-2012.

Time	Overall VTE n Cum. Inc. (95% CI)	Cancer-related VTE n Cum. Inc. (95% CI)	Provoked VTE* n Cum. Inc. (95% CI)	Unprovoked VTE n Cum. Inc. (95% CI)
1 day	2 0.2 (0.1-1.1)	-	1 0.42 (0.1-2.9)	1 0.3 (0.1-2.4)
7 days	6 0.8 (0.3-1.9)	1 0.6 (0.1-4.4)	3 1.3 (0.1-3.8)	2 0.7 (0.2-3.0)
1 month	12 1.7 (0.01-3.1)	4 2.7 (1.0-7.0)	5 2.1 (1.0-5.0)	3 1.0 (0.3-3.1)
3 months	18 2.7 (1.7-4.3)	5 3.7 (1.5-8.9)	9 4.0 (2.0-7.4)	4 2.0 (0.5-4.0)
6 months	27 4.3 (3.0-6.2)	9 8.2 (4.3-15.7)	11 5.0 (3.0-9.0)	7 2.5 (1.2-5.1)
1 year	43 7.3 (5.4-9.7)	15 16.3 (9.9-25.9)	16 7.4 (4.6-11.8)	12 4.7 (3.0-8.0)
2 years	64 11.6 (9.1-14.6)	18 22.0 (14.0-34.0)	20 10.2 (6.7-15.2)	26 10.0 (7.0-14.4)
5 years	90 18.8 (15.4-22.8)	19 26.4 (16.2-41.0)	30 16.7 (11.8-23.2)	41 17.9 (13.4-24.0)
7 years	97 21.6 (17.8-26.0)	19 26.3 (16.2-41.0)	34 20.4 (14.7-27.8)	44 21.0 (16.0-27.0)
10 years	108 28.3 (23.3-33.9)	19 26.3 (16.2-41.0)	38 25.8 (18.8-34.7)	51 30.3 (23.0-39.3)

Abbreviations: VTE = venous thromboembolism, n= number of cases, CI = confidence interval.

* Without cancer.

Supplementary table 2 Cumulative incidence of all-cause mortality according to time since VTE and classification of the index event. The Tromsø Study 1994-2012.

Time	Overall VTE Deaths Cum. Inc (95% CI)	Cancer-related VTE Deaths Cum. Inc (95% CI)	Provoked VTE* Deaths Cum. Inc (95% CI)	Unprovoked VTE Deaths Cum. Inc (95% CI)
1 day	22 3.1 (2.1-4.6)	7 4.2 (2.0-8.6)	13 5.2 (3.1-8.8)	2 0.7 (0.2-2.6)
7 days	30 4.2 (2.9-6.0)	8 4.8 (2.4-9.4)	18 7.2 (4.6-11.2)	4 1.3 (0.5-3.5)
1 month	61 8.6 (6.7-11.0)	32 19.4 (14.1-26.3)	22 9.0 (5.9-13.1)	7 2.3 (1.1-4.9)
3 months	114 16.2 (13.6-19.1)	69 42.6 (35.4-50.6)	32 12.9 (9.3-17.7)	13 4.4 (2.6-7.5)
6 months	134 20.0 (16.3-22.1)	79 48.9 (41.5-56.9)	40 16.2 (12.1-21.4)	15 5.1 (3.1-8.3)
1 year	169 24.2 (21.2-27.6)	99 62.0 (54.3-69.4)	48 19.6 (15.1-25.2)	22 7.5 (5.0-11.2)
2 years	210 30.6 (27.3-34.2)	116 74.1 (66.9-80.8)	61 25.9 (20.8-32.0)	33 11.5 (8.3-15.8)
5 years	264 40.1 (36.5-44.1)	132 86.3 (79.8-91.6)	76 32.9 (27.2-39.5)	56 21.3 (16.8-26.9)
7 years	296 47.6 (43.6-52.0)	133 88.3 (81.3-93.6)	91 42.6 (36.0-49.8)	72 30.1 (24.5-36.6)
10 years	320 55.4 (50.9-59.9)	133 88.3 (81.3-93.6)	99 50.7 (43.2-58.6)	88 41.5 (34.7-49.1)

Abbreviations: VTE = venous thromboembolism, CI = confidence interval.

* Without cancer.