

## ORIGINAL ARTICLE

# Hospital-related first venous thromboembolism and risk of recurrence

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## Essentials

- Recurrence risk after a hospital-related venous thromboembolism (VTE) is underinvestigated.
- We explored this association in a cohort of patients with a first VTE from the Tromsø study.
- Stratification on hospital-related factors revealed considerable differences in recurrence risk.
- The recurrence risk was high in cases with a VTE related to hospitalization for medical illness.

**Summary.** *Background:* Hospitalization is a well-established risk factor for first venous thromboembolism (VTE), but the risk of recurrence, particularly in patients hospitalized for conditions other than cancer or surgery, has scarcely been investigated. The cumulative incidence of recurrence in hospital-related VTE may be influenced by the competing risk of death. *Objectives:* To investigate the risk of recurrence and mortality among patients with a first hospital-related VTE in models with and without death as a competing event. *Methods:* Information on hospital-related risk factors was collected in 822 patients with a first-lifetime VTE derived from the Tromsø study. Recurrent VTEs and deaths were recorded during follow-up (1994–2012). *Results:* During a median of 2.79 years of follow-up, 132 patients experienced a recurrent VTE. Stratification on hospital-related factors revealed considerable differences in recurrence risk. The 5-year cumulative incidence of recurrence was 27.4%, 11.0% and 20.1% in patients with incident VTEs related to cancer, surgery or other medical illness, respectively, and 18.4%

in patients with a non-hospital-related first VTE. The mortality rates were high for all subgroups of hospital-related VTE, except for surgery-related events. Consequently, the cumulative incidence of recurrence dropped in the competing risk analyses, showing a 5-year cumulative incidence of 14.4%, 11.7% and 9.7% in patients with a first VTE related to hospitalization for other medical illness, cancer or surgery, respectively. *Conclusions:* Our findings suggest that patients with incident VTEs related to hospitalization for medical illness other than cancer or surgery have a high recurrence-risk, even in the presence of competing risk of death.

**Keywords:** epidemiology; hospitalization; recurrence; risk factors; venous thromboembolism.

## Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively referred to as venous thromboembolism (VTE), are frequently associated with considerable morbidity and mortality [1–3]. VTE is particularly common among hospitalized patients, with incidence rates (IRs) exceeding 100 times greater than those in community residents [4]. Moreover, 40–50% of the VTE cases can be attributed to hospitalization, with hospitalization for surgery and medical illness accounting for similar proportions [5].

After an incident episode of VTE, 30–40% experience a recurrent event within 10 years, and the risk is highest during the first 6–12 months [2,6–9]. The risk of recurrence is dependent on the clinical characteristics of the initial event. Patients with a first VTE provoked by a transient risk factor (e.g. surgery) are at low risk of recurrence [6,8,10–13], whereas VTEs provoked by a persistent risk factor, such as active cancer, have a high risk of recurrence [6,8,12,14,15]. When no provoking risk factor (transient or persistent) can be identified, the event is classified as unprovoked, and these patients have an intermediate to high risk of recurrence [9–13,16,17]. However,

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categorization along this continuum may be difficult, particularly for patients where considerable uncertainty exists regarding the prognostic importance of a risk factor.

Hospitalization in itself is an interim exposure and may therefore be considered as a transient risk factor, assumed to yield a low risk of recurrence. However, the risk of recurrence after a first hospital-related VTE, particularly hospitalization for conditions other than cancer or surgery, has not been extensively studied. Moreover, as the mortality rate is expected to be higher among patients with co-morbidity, the cumulative incidence of recurrence may be influenced by the competing risk of death, particularly in these patients [18]. In the present study, we therefore aimed to investigate the risk of recurrence and mortality among patients with a first hospital-related VTE, and to compare the impact of transient and persistent hospital-related factors such as surgery, cancer or other medical conditions on the risk of recurrence in models with and without death as a competing event.

## Methods

### Study population

The source population comprised subjects participating in the first (1974), second (1979/80), third (1986/87), fourth (1994/95), fifth (2001/02) and sixth (2007/08) surveys of the Tromsø study. The Tromsø study is a single-center, population-based, prospective cohort study, with repeated health surveys of inhabitants in the municipality of Tromsø in the north of Norway. Further details about the Tromsø study can be found elsewhere [19]. The Regional Committee of Medical and Health Research Ethics approved the study, and written consent was collected from all participants. Overall, 39 825 unique individuals, aged 25–97 years, participated in at least one of the surveys, which yielded an average participation rate of 78.5% for all surveys. Participants that were still alive and living in the municipality of Tromsø by 1 January 1994 ( $n = 33\,885$ ) were followed through to 31 December 2012, and all potential cases of first lifetime VTE were identified by searching the hospital discharge diagnosis registry, the autopsy registry and the radiology procedure registry at the University Hospital of North of Norway. This is the only hospital in the region and serves as the exclusive provider of all diagnostic radiology procedures and VTE-related healthcare in the area. Trained personnel reviewed the medical records for each potential VTE case and extracted information for case-validation. A VTE event was considered verified and recorded when presence of clinical signs and symptoms of DVT or PE were combined with objective confirmation tests (compression ultrasonography, venography, spiral computed tomography, perfusion-ventilation scan, pulmonary angiography and autopsy) and resulted in a VTE diagnosis that required treatment, as previously described [20].

Using the criteria described above, 822 subjects with a validated first lifetime VTE event were identified and included in our study.

### Patient characteristics

Information on clinical and provoking factors at the time of and 8 weeks preceding the VTE event, were extracted by review of medical records using standardized forms. We defined a VTE as being hospital related when patients were hospitalized within 8 weeks preceding the VTE (including patients hospitalized at the time of VTE), had undergone surgery (with or without subsequent hospitalization) within 8 weeks preceding the event or had active cancer. When none of these factors could be identified, the event was classified as non-hospital-related. Cancer was registered as the provoking factor only when patients had active cancer at the time of the initial event. Bedrest was defined as confinement to bed in hospital > 3 days, whereas other immobilization was defined as transient or persistent use of a wheelchair or long haul travel > 4 h (i.e. by airplane, train, car or boat). Hospital-related VTE was classified into three main categories according to the main provoking factor for the first VTE following the algorithm: cancer > surgery > hospitalization for other medical illness.

Clinical factors included were obesity, use of estrogens, family history of VTE, pregnancy, puerperium or other co-morbidities. Participants were classified as obese according to the World Health Organization definition ( $\text{BMI} > 30 \text{ kg m}^{-2}$ ) [21]. Co-morbidity was defined as a myocardial infarction or a stroke within the last 12 months preceding the VTE, chronic obstructive pulmonary disease (COPD), myeloproliferative disorders, systemic lupus erythematosus or a chronic infection.

### Outcomes

All cases of recurrent VTE were recorded in the period 1994–2012. The diagnosis of recurrent VTE was made using the same criteria as described for validating first lifetime VTE events. Information on mortality was collected from the Norwegian Population Registry.

### Statistics

Statistical analyses were performed using STATA version 14.0 (Stata Corporation LP, College Station, TX, USA). The significance level was set to 0.05. For analyses of recurrence, subjects were followed from the date of their first VTE to the first occurring event of a recurrent VTE ( $n = 132$ ), death ( $n = 307$ ), loss to follow-up as a result of migration ( $n = 19$ ) or end of follow-up (31 December 2012) ( $n = 364$ ). Crude IRs of recurrent VTE were calculated and expressed per 100 person-years at risk. Kaplan–Meier failure estimates were calculated and visualized according to hospital-related classification of the first

VTE (no hospitalization, cancer, surgery or hospitalization because of other medical conditions). Moreover, Cox proportional hazards regression models were performed to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) of VTE recurrence according to individual characteristics associated with the incident VTE event. The HRs were estimated in two models, allowing for adjustment of the other provoking factors in those with multiple provoking factors. Model 1 included age and sex, and Model 2 was a multivariable model that included age, sex and all the characteristics of interest (i.e. surgery, acute medical condition, cancer and bedrest > 3 days). Furthermore, crude mortality rates per 100 person-years and HRs of death were calculated using the same models as described above. The proportional hazards assumption was tested for all variables using Schoenfeld residuals.

Generally, hospitalized patients have poorer prognosis than outpatients and healthy subjects. Because the mortality rates were likely to differ among those with and without hospital-related factors, the rates of VTE recurrence in these patients could potentially be overestimated as a result of competing risk of death. In order to account for death as a competing event, cumulative incidence functions were performed and visualized using the user-contributed *stcompet* suite and the *sterreg* cif curve in STATA (Stata Corporation LP).

## Results

Of the 822 patients with validated first lifetime VTE, 19 died on the same day as the VTE occurred and were therefore excluded from follow-up. The baseline characteristics and the distribution of risk factors among patients with and without hospital-related first VTE are shown in Table 1. The patients with hospital-related VTE were on average 4 years older (mean age =  $68.9 \pm 13.5$  vs.  $64.9 \pm 14.7$ ) and more likely to be female (54.4% vs. 49.5%) than those with a non-hospital-related VTE. Only 1.0% of the hospital-related events occurred in patients with a reported history of first-degree relatives suffering from a VTE before age 60, whereas 5.9% of the non-hospital-related events occurred in patients with a known family history of VTE. Furthermore, co-morbid conditions were more common among the hospital-related events as opposed to the non-hospital-related events (24.3% vs. 18.8%). The durations of anticoagulant treatment within subgroups of patients with hospital-related VTE are shown in Table S1.

### Recurrence

During the course of 3423 person-years of follow-up, 132 subjects experienced a recurrent episode of VTE. The mean observation time was 4.3 years, ranging from 1 day to 18.8 years. The overall crude IR of recurrence was 3.9 per 100 person-years (95% CI, 3.3–4.6). Characteristics of the

**Table 1** Characteristics of subjects with hospital-related and non-hospital-related first venous thromboembolism

	Hospital-related	
	Yes ( <i>n</i> = 412)	No ( <i>n</i> = 410)
Age (years)	68.9 ± 13.5	64.9 ± 14.7
Sex (% women)	54.4	49.5
Obesity (% obese)	15.5	18.8
Location at onset		
Hospital	38.3	–
Nursing home	2.9	4.4
Community	58.8	95.6
Deep vein thrombosis	59.2	57.6
Pulmonary embolism	40.8	42.4
Treatment duration with AC		
0–3 months	36.4	16.8
3–6 months	36.7	48.0
6–12 months	20.6	27.6
> 12 months	6.3	7.6
Clinical risk factors		
Estrogens	3.4	8.3
FHVTE	1.0	5.9
Co-morbidity	24.3	18.8
Pregnancy/postpartum	0.7	0.7
Surgery	31.1	0
Trauma	9.5	7.0
Acute medical condition	21.6	5.6
Cancer	46.4	0
Confined to bed > 3 days	11.9	1.5
Other immobilization	15.8	7.6
Other provoking factor	7.0	2.9

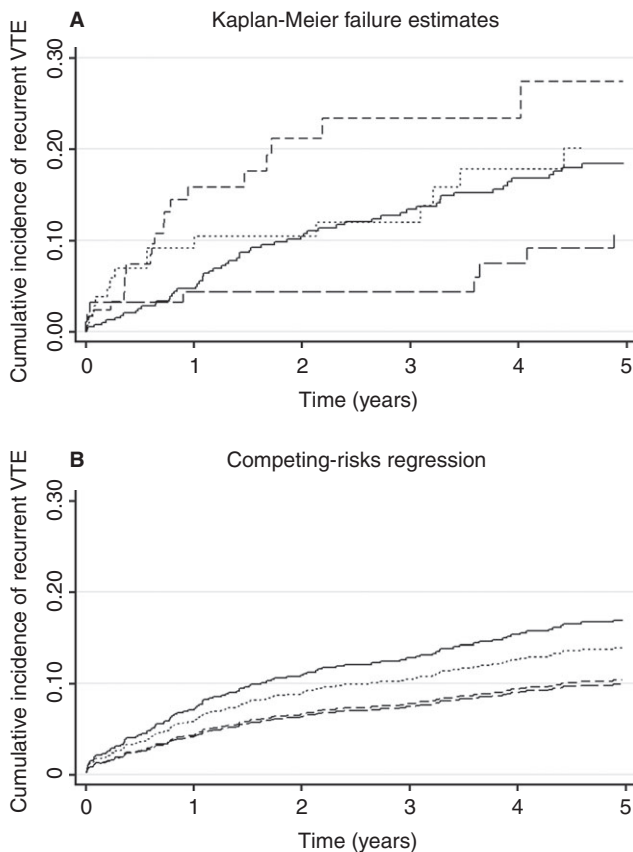
Values are means ± 1 SD or percentages. AC, anticoagulants; FHVTE, family history of venous thromboembolism.

VTE recurrences are shown in Table S2. A hospital-related VTE *per se* was not associated with increased risk of recurrent thrombosis (HR, 0.99; 95% CI, 0.69–1.41) in the age- and sex-adjusted model (Table 2). However, the recurrence risk varied greatly according to the classification of the first hospital-related event (Fig. 1A). After 5 years of follow-up, the cumulative incidence of recurrence was 27.4% (95% CI, 17.3–41.6) in patients with a first VTE associated with cancer. Patients with a surgery-related first VTE had the lowest risk of recurrence after 5 years (11.0%; 95% CI, 5.5–21.1), whereas patients hospitalized because of other medical illness and non-hospital-related first events had a 20.1% (95% CI, 12.2–32.0) and 18.4% (95% CI, 14.5–23.1) cumulative recurrence risk after 5 years, respectively. The recurrence rate was highest during the first 12 months, especially for cancer-related events and events associated with other medical illness. When this relationship was expressed in a Cox proportional hazard model (Table 2), cancer patients had a 73% higher risk of recurrence (HR, 1.73; 95% CI, 1.06–2.81) and patients with surgery-associated events had 47% lower risk of recurrence (HR, 0.53; 95% CI, 0.28–0.99) than those without hospital-related events. Patients hospitalized with a medical illness other than cancer or surgery appeared to have similar risk of recurrence (HR, 1.02; 95% CI, 0.61–1.72) to those with a

**Table 2** Incidence rates and risk of recurrent venous thromboembolism (VTE) by classification of hospital-related first VTE

	<i>n</i>	Recurrences	IR (95% CI)*	HR (95% CI)†
Non-hospital-related	410	81	3.7 (3.0–4.6)	Reference
Hospital-related‡	412	51	4.1 (3.1–5.4)	0.99 (0.69–1.41)
Cancer-related	191	22	8.8 (5.8–13.3)	1.73 (1.06–2.81)
Surgery-related	97	11	1.9 (1.0–3.4)	0.53 (0.28–0.99)
Other medical illness	124	18	4.7 (3.0–7.4)	1.02 (0.61–1.72)

CI, confidence interval; HR, hazard ratio; IR, incidence rates. \*Per 100 person-years. †Adjusted for age and sex. ‡Hospital-related includes patients hospitalized within 8 weeks preceding the VTE, who are further classified into three main categories according to the main provoking factor following the algorithm: cancer > surgery > hospitalization for other medical illness.



**Fig. 1.** Cumulative incidence of venous thromboembolism (VTE) recurrence according to classification of the first VTE event in crude analyses (A) and with death as a competing event (B). —, non-hospital-related; ---, cancer related; — — —, surgery-related; ·····, other medical illness.

non-hospital-related VTE. Further adjustment for duration of anticoagulant treatment did not influence the risk estimates (data not shown).

The IRs and HRs of VTE recurrence according to individual characteristics associated with the first VTE are presented in Table 3. In the multivariable model, in which all characteristics were mutually adjusted for, surgery was significantly associated with decreased risk of VTE recurrence, displaying a 61% (HR, 0.39; 95% CI, 0.21–0.71) lower risk compared with those without a surgery-associated first VTE (Table 3). Cancer, on the other hand,

was significantly associated with an almost 2-fold increased risk of recurrence in this model (HR, 1.95; 95% CI, 1.21–3.15).

### Mortality

In total, 442 patients died during the course of 3896 person-years of follow-up. Estimated mortality rates and HRs of death according to classification of the first event are shown in Table 4. Overall, patients with a hospital-related VTE had a 2.8-fold higher risk of death (HR, 2.76; 95% CI, 2.26–3.37). Compared with non-hospital-related events, patients with a first VTE event related to cancer or other medical illness had a 7.4-fold and 2.2-fold higher risk of death, respectively (HR, 7.39; 95% CI, 5.84–9.35; and HR, 2.20; 95% CI, 1.68–2.88), whereas patients with a first VTE event related to surgery had a 13% lower risk of death (HR, 0.87; 95% CI, 0.60–1.26). In multivariable analyses of the individual components, cancer (HR, 6.09; 95% CI, 4.95–7.49), bedrest > 3 days (HR, 2.47; 95% CI, 1.77–3.46) and acute medical conditions (HR, 1.36; 95% CI, 1.05–1.78) were all significantly associated with increased risk of death (Table 5).

### Competing risk of death

Cumulative incidence functions (Fig. 1B) showed that patients with a non-hospital-related first VTE had the highest risk of recurrence, with a cumulative incidence of 16.4% (95% CI, 12.8–20.4) after 5 years, when death was included as a competing event. In comparison, patients with other medical illness had a cumulative incidence of 14.4% (95% CI, 8.4–21.9) after 5 years, whereas cancer and surgery-related events had a similar cumulative incidence of 11.7% (95% CI, 7.6–17.0) and 9.7% (95% CI, 4.5–17.4) after 5 years, respectively. Sub-distribution HRs of VTE recurrence according to characteristics associated with the first VTE are shown in Table 3.

### Discussion

In the present study, subjects with a hospital-related first VTE had a similar risk of recurrence to those with a non-hospital-related VTE. However, Kaplan–Meier failure

**Table 3** Incidence rates and risk of venous thromboembolism (VTE) recurrence according to individual characteristics associated with the first VTE

	Recurrences	IR (95% CI)*	Model 1† HR (95% CI)	Model 2‡ HR (95% CI)	SHR (95% CI)†
Surgery	12	1.8 (1.0–3.2)	0.45 (0.25–0.81)	0.39 (0.21–0.71)	0.52 (0.28–0.93)
Acute medical condition	18	5.7 (3.6–9.0)	1.35 (0.82–2.22)	1.32 (0.78–2.25)	1.10 (0.66–1.84)
Bedrest > 3 days	7	6.6 (3.1–13.7)	1.66 (0.78–3.57)	1.85 (0.81–4.21)	0.83 (0.38–1.83)
Cancer	22	8.8 (5.8–13.3)	1.87 (1.17–2.99)	1.95 (1.21–3.15)	0.66 (0.41–1.06)

CI, confidence interval; HR, hazard ratio; IR, incidence rate; SHR, sub-distribution hazard ratio (competing risk analysis). \*Per 100 person-years. †Model 1: adjusted for age and sex. ‡Model 2: adjusted for surgery, acute medical condition, bedrest > 3 days, cancer, age and sex.

**Table 4** Mortality rates and risk of death by classification of hospital-related first venous thromboembolism

	n	Deaths	MR (95% CI)*	HR (95% CI)†
Non-hospital-related	410	148	5.8 (4.9–6.8)	Reference
Hospital-related‡	412	294	21.9 (19.5–24.5)	2.76 (2.26–3.37)
Cancer	191	171	65.5 (56.4–76.1)	7.39 (5.84–9.35)
Surgery	97	34	5.4 (3.8–7.5)	0.87 (0.60–1.26)
Other medical illness	124	89	19.8 (16.1–24.4)	2.20 (1.68–2.88)

CI, confidence interval; HR, hazard ratio; MR, mortality rates. \*Per 100 person-years. †Adjusted for age and sex. ‡Hospital-related includes patients hospitalized within 8 weeks preceding venous thromboembolism, who are further classified into three main categories according to the main provoking factor following the algorithm: cancer > surgery > hospitalization for other medical illness.

estimates revealed considerable heterogeneity among the hospital-related events with regards to recurrence risk. Patients with index events related to hospitalization for medical illness other than surgery or cancer had a similar risk of recurrence to patients with a non-hospital-related first VTE after 5 years of follow-up. In accordance with previous studies [6,8,10–13,15], patients with cancer-related first events were found to have a high risk of recurrence, whereas patients with surgery-related first episodes of VTE had a low risk of recurrence after 5 years of follow-up. A hospital-related first VTE was associated with a 3-fold higher risk of death compared with non-hospital-related VTE, and except for surgery-related events, all subgroups of hospital-related VTE displayed an increased mortality-risk. Consequently, the cumulative

recurrence rates decreased when competing risk of death was taken into account. This was particularly pronounced for cancer-related VTE, which was lower than the cumulative risk among non-hospital-related cases and events related to hospitalization for other medical illnesses.

The IR of VTE among hospitalized patients is > 100-fold higher than among community residents [4] and the risk of a first VTE is significantly increased during the initial 3-month period after a hospital stay [8]. For transient risk factors, the risk of VTE recurrence is generally low as long as the risk factor is removed and the effect of the risk factor is reversible [8,11,12]. Thus, the transient nature of hospitalization could imply a low recurrence risk among those with a first hospital-related VTE. In our study, however, hospitalization within 8 weeks preceding an incident VTE event, including patients admitted at the time of the event, was not associated with a lower risk of recurrence. Accordingly, a previous study of 1791 patients with a first VTE recruited and followed in the period 1966–1990, showed no association between recent hospitalization (3 months preceding the first VTE) and risk of recurrence (HR, 1.01) [8].

Although the recurrence risk did not differ among hospital-related and non-hospital-related first VTEs, the reason for hospitalization preceding the first event appeared to have a major impact on recurrence risk. As shown in previous studies [6,8,10–12,14–16], surgery, a transient and reversible risk factor, was associated with a low risk of recurrence in both conventional and competing risk analyses. Cancer, a persistent and mostly irreversible risk factor, was associated with a high risk of recurrence in conventional Kaplan–Meier analyses. However, competing risk analyses revealed that this risk was substantially

**Table 5** Mortality rates and risk of death according to individual characteristics associated with the first venous thromboembolism

	Deaths	MR (95% CI)*	Model 1† HR (95% CI)	Model 2‡ HR (95% CI)
Surgery	60	8.5 (6.6–10.9)	0.77 (0.59–1.02)	0.62 (0.47–0.82)
Acute medical condition	84	23.1 (18.7–28.6)	1.72 (1.35–2.18)	1.36 (1.05–1.78)
Bedrest > 3 days	47	40.9 (30.7–54.4)	3.01 (2.21–4.09)	2.47 (1.77–3.46)
Cancer	171	65.5 (56.4–76.1)	6.09 (4.95–7.49)	6.09 (4.94–7.51)

CI, confidence intervals; HR, hazard ratio; MR, mortality rate. \*Per 100 person-years. †Model 1: adjusted for both age and sex. ‡Model 2: adjusted for surgery, acute medical condition, bedrest > 3 days, cancer, age and sex.

overestimated as a result of the high mortality rate among cancer patients.

Whether hospitalization for medical illnesses other than cancer or surgery should be regarded as a temporary risk condition with a low recurrence risk is not well studied. Heit and colleagues [22] found a non-significant 15% increased risk of recurrence among those with a first VTE related to hospitalization for acute medical illness compared with all other VTEs (i.e. hospitalized for other conditions and non-hospitalized). A study of 1626 VTE patients followed for a median of 50 months after withdrawal of anticoagulation, reported that patients who had been bedridden for > 1 week because of a medical disease preceding the first VTE were more likely to develop recurrence than those with recent trauma or surgery [9]. However, this study did not distinguish between hospitalized and non-hospitalized patients. In our study, we showed that patients with a first VTE related to hospitalization for medical illness other than cancer or surgery had similar risk of recurrence to subjects with a non-hospital-related VTE, and that the cumulative incidence of recurrence remained high even after the competing risk of death was taken into account.

The relatively high rates of recurrence after a first VTE related to hospitalization for a medical illness point towards a persistent nature of the VTE risk in these subjects. Several chronic conditions, such as chronic heart and lung diseases, as well as inflammatory and autoimmune disorders, are associated with coagulation and fibrinolytic abnormalities [23–27], endothelial dysfunction [23–27], increased platelet activation [24,25,27] and inflammation [23–25,27], which may induce a prothrombotic state. Moreover, disease-specific mechanisms, such as hypoxia in COPD patients [24] and right ventricular failure with subsequent venous stasis in patients with congestive heart failure, [25,26] may add to the VTE risk, and flare-up periods [27–29] or exacerbations [30,31] that lead to re-hospitalization may induce additional prothrombotic risk factors, such as immobilization. The latter is supported by Heit *et al.* [22], who studied hospitalization as an interim exposure after a first VTE and found that patients hospitalized for a medical illness had an almost 6-fold increased risk of VTE recurrence during the hospital stay, and a 2.6-fold increased risk within 92 days post-dismissal.

Previous studies have shown both in-hospital and post-hospital discharge [32], as well as cancer and several other medical co-morbidities, to be associated with high mortality rates after a first VTE [1,7,33,34], whereas the opposite findings have been reported for various types of surgery [33]. Accordingly, in the present study, increased mortality rates were found for all subgroups of VTE patients, except for those with surgery-related events. Our estimated 6.1-fold higher mortality risk among cancer patients vs. cancer-free subjects is consistent with previous studies in which risk estimates ranging from 4.5 to 9.5 were reported [1,7,33,34]. Moreover, our findings of a 2-fold increased

risk of death among patients with acute medical conditions is in agreement with previous studies showing that heart diseases, neurologic diseases and chronic lung, renal and liver diseases are associated with a 2- to 4-fold increased risk of death in patients with VTE [33,35,36].

In the presence of competing risk of death, the cumulative incidence of recurrence is dependent on both the hazard of recurrence and the hazard of dying, and consequently, recurrence risks are overestimated when the mortality rate is high [37–39]. Accordingly, the cumulative incidences of recurrence were lower in all subgroups after competing risk analysis in our study. In patients with a first VTE related to hospitalization for medical illness, the 5-year cumulative recurrence dropped from 20.1% to 14.4%, suggesting a moderate role of hospital-related mortality in estimating recurrence risk among these patients. The change was much more pronounced in cancer patients (dropped from 27.4% to 11.7%), and the 5-year cumulative incidence was comparable to that of surgery-related first VTE (11.7% vs. 9.7%). This result is in contrast to the study by Heit *et al.* [22], which reported a 5-year cumulative incidence of 34% in cancer-related VTE and 17% in secondary non-cancer VTE (including subjects hospitalized for surgical or medical conditions) in competing risk analysis. The diverging results may in part be explained by the vast difference in mortality rates between the studies, particularly among cancer patients, as well as differences in the length of follow-up and definition of active cancer.

Current guidelines recommend short-term (3 months) anticoagulant treatment over longer-term treatment in patients with a DVT or PE provoked by a non-surgical transient risk factor [40]. Although hospitalization for a medical condition other than cancer or surgery is a transient condition, the high recurrence risk among these patients suggests a more persistent underlying VTE risk that may justify similar treatment recommendations to those for unprovoked VTE, as well as increased awareness of recurrence risk in high-risk situations such as re-hospitalization.

The strengths of the present study include the recruitment of patients with first VTE from a general population, the prospective design and long-term follow-up. Because a single hospital serves the entire study population the chance of missing outcomes is very low. Moreover, the combination of multiple approaches to identify cases, comprehensive medical records review and firm criteria for VTE assessment yields thorough validation of first and recurrent VTE events. Advances in prevention, diagnosis and treatment of VTE may have influenced outcomes during the last two decades and our data have the advantage of being collected from a recent time period compared with previous studies [6,8,22]. The study has limitations. Information on patient characteristics was collected from medical records and relied on the reporting by physicians, nurses and other healthcare professionals. However, the main exposures in this study are major

clinical events for which one would expect a low degree of under-reporting and misclassification. Unfortunately, because of the low number of events we had limited statistical power in subgroups and our findings should therefore be interpreted with caution. Moreover, we did not have the possibility to further investigate the recurrence risk among different disease entities in patients with a first VTE related to hospitalization for medical illness.

In conclusion, the risk of recurrence after a hospital-associated first VTE appeared to be dependent on the reason for hospitalization. However, except for surgery-related VTE, this did not hold true in the competing risk analysis. Our findings suggest that patients suffering from incident VTEs associated with hospitalization for medical illness other than cancer or surgery have a high risk of recurrence, even after competing risk of death is taken into account.

### Addendum

E. Bjøri was responsible for data analysis and writing the manuscript. N. Arshad was responsible for data interpretation and revising the manuscript. H. S. Johnsen was responsible for data interpretation and revising the content. J.-B. Hansen was responsible for the conception and design of the study, data collection and interpretation, and writing the manuscript. S. K. Brækkan was responsible for the conception and design of the study, data collection and interpretation, and writing the manuscript.

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### Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

### Supporting Information

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

**Table S1.** Duration of anticoagulant therapy stratified by subgroups of venous thromboembolism (VTE).

**Table S2** Characteristics of recurrent venous thromboembolism (VTE) in patients with hospital-related and non-hospital-related first VTE.

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## Supplementary Material

**Table 1** Duration of anticoagulant therapy stratified by subgroups of VTE.

	<b>Cancer (n=191)</b>	<b>Surgery (n=97)</b>	<b>OMI (n=124)</b>
0-3 months	42.4	31.9	30.6
3-6 months	30.4	43.3	41.1
6-12 months	18.8	22.7	21.8
> 12 months	8.4	2.1	6.5

Values are percentages. AC anticoagulants; OMI Other Medical Illnesses; VTE venous thromboembolism

**Table 2** Characteristics of Recurrent VTE in patients with Hospital- and Non Hospital Related first VTE.

	Hospital-related	
	Yes (n=51)	No (n=81)
Age (years)	71.3 ± 11.1	67.2 ± 14.0
Sex (% women)	58.8	39.5
Obesity (% Obese)	5.9	23.5
Location at onset		
Hospital	27.5	9.9
Nursing home	2.0	6.2
Community	70.5	83.9
Deep Vein Thrombosis	64.7	55.6
Pulmonary Embolism	35.3	44.4
Clinical risk factors		
Estrogens	2.0	1.2
FHVTE	-	7.4
Comorbidity	31.4	13.6
Pregnancy/Post partum	-	-
Surgery	13.7	8.6
Trauma	3.9	2.5
Acute medical condition	17.6	7.4
Cancer	47.0	9.9
Confined to bed > 3 days	11.8	2.5
Other immobilization	5.9	11.1
Other provoking factor	7.8	6.2

Values are means ± 1 SD or percentages. AC anticoagulants; FHVTE family history of VTE; VTE venous thromboembolism