# Epidemiology of first and recurrent venous thromboembolism: A population-based cohort study in patients without active cancer

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**Summary**

Contemporary data from population studies on the incidence and complications of venous thromboembolism (VTE) are limited. An observational cohort study was undertaken to estimate the incidence of first and recurrent VTE. The cohort was identified from all patients in the UK Clinical Practice Research Datalink (CPRD) with additional linked information on hospitalisation and cause of death. Between 2001 and 2011, patients with first VTE were identified and the subset without active cancer-related VTE observed for up to 10 years for recurrent VTE. The 10-year cumulative incidence rates (CIR) were derived with adjustment for mortality as a competing risk event. A total of 35,373 first VTE events (12,073 provoked, 16,708 unprovoked and 6592 active cancer-associated VTE) among 26.9 million person-years of observation were identified. The overall incidence rate (IR) of VTE was 131.5 (95% CI, 130.2–132.9) per 100,000 person-years and 107.0 (95% CI, 105.8–108.2) after excluding cancer-associated VTE. DVT was more common in the young and PE was more common in the elderly. VTE recurrence occurred in 3671 (CIR 25.2%). The IR for recurrence peaked in the first six months at around 11 per 100 person years. It levelled out after three years and then remained at around 2 per 100 person years from year 4–10 of follow-up. The IRs for recurrences were particularly high in young men. In conclusion, VTE is common and associated with high recurrence rates. Effort is required to prevent VTE and to reduce recurrences.

**Keywords**

Thrombosis, pulmonary embolism, deep-vein thrombosis

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Received: September 24, 2013
Accepted after major revision: February 27, 2014
Epub ahead of print: April 3, 2014

**http://dx.doi.org/10.1160/TH13-09-0793**
**Thromb Haemost 2014; 112: 255–263**

## Introduction

Venous thromboembolism (VTE), comprising deep-vein thrombosis (DVT) and pulmonary embolism (PE), is an important cause of morbidity and mortality in patients with various medical and surgical conditions, and in previously healthy patients. It is the third most common cause of cardiovascular disease after myocardial ischemia and stroke (1, 2).

In Western countries population studies have reported incidence rates of VTE between 80–180 per 100,000 person-years, with the variations likely due to a number of reasons including case definition, study design and age restriction (3-5). Autopsy studies have suggested that the incidence of the most serious complication of VTE, fatal PE, could be underestimated in population studies (6). For almost a quarter of PE patients the initial clinical presentation is sudden death (4). As out of hospital diagnosis and therapy is becoming more frequent, study populations need to include outpatients to assess the burden of VTE (7).

The outlook after an episode of symptomatic VTE can be blighted by long-term sequelae including recurrence of VTE. VTE may be associated with risk factors and is classified as provoked (within three months following a recognised event), cancer-related and unprovoked (idiopathic) (5, 7). Our objective was to estimate the incidence rate of first VTE events in the general population, and its subsequent risk of recurrence in patients without active cancer using data from primary care, hospital discharge diagnoses and death certificates.

## Material and methods

This study used data obtained from the subset of the United Kingdom Clinical Practice Research Datalink (CPRD), until March 2012 known as the General Practice Research Database, linked to the Hospital Episodes Statistics (HES) and to the Office for National Statistics (ONS) Mortality data (8, 9). CPRD is based on primary care and includes demographics, medical history, symptoms and diagnoses recorded with Read medical codes, unstructured medical notes, letters to and from secondary care and prescriptions issued by the general practitioner (GP). CPRD has been validated in VTE research (10). HES include dates of hospital admission and discharge, primary and other main reasons for treatment recorded with ICD-10, and surgical operations and procedures performed during hospital stay. ONS data contain the date and cause of death as recorded as ICD-10 in death certificates.

To identify a cohort with incident VTE the study cohort was formed from all individuals in the CPRD/HES and ONS-datalink.

The start of observation for all subjects was defined by the latest of January 1, 2001 or completion of a one-year registration period in CPRD. Patients were followed over time until the earliest of the following time points: October 31, 2011, the date of DVT/PE, the patient died or transferred out of the practice, or the end of data collection of GP practice or the completion of a 10-year observational period following first VTE event.

Ethnic origin was available from the subset of the source population with any hospital admission recorded. To avoid possible racial diagnostic bias, we only analysed the subset with at least one non-VTE related hospitalisation to estimate ethnic-specific incidence rates.

## Algorithm for first VTE events

First VTE events were identified from death, hospital episodes or primary care-managed episodes using respective medical and procedure codes from ONS, HES and CPRD and by searching medical notes recorded in the CPRD for word strings indicative of VTE. All identified and anonymised notes were manually reviewed by two of us (ATC and CM).

VTE comprised PE and DVT. DVT included thrombosis of the deep veins of the legs, calf vein thrombosis, thrombosis of pelvic veins and vena cava as well as thrombosis of the upper limb. Cerebral and abdominal vein thrombi were excluded from this cohort. Patients with isolated calf vein thrombosis were only included in

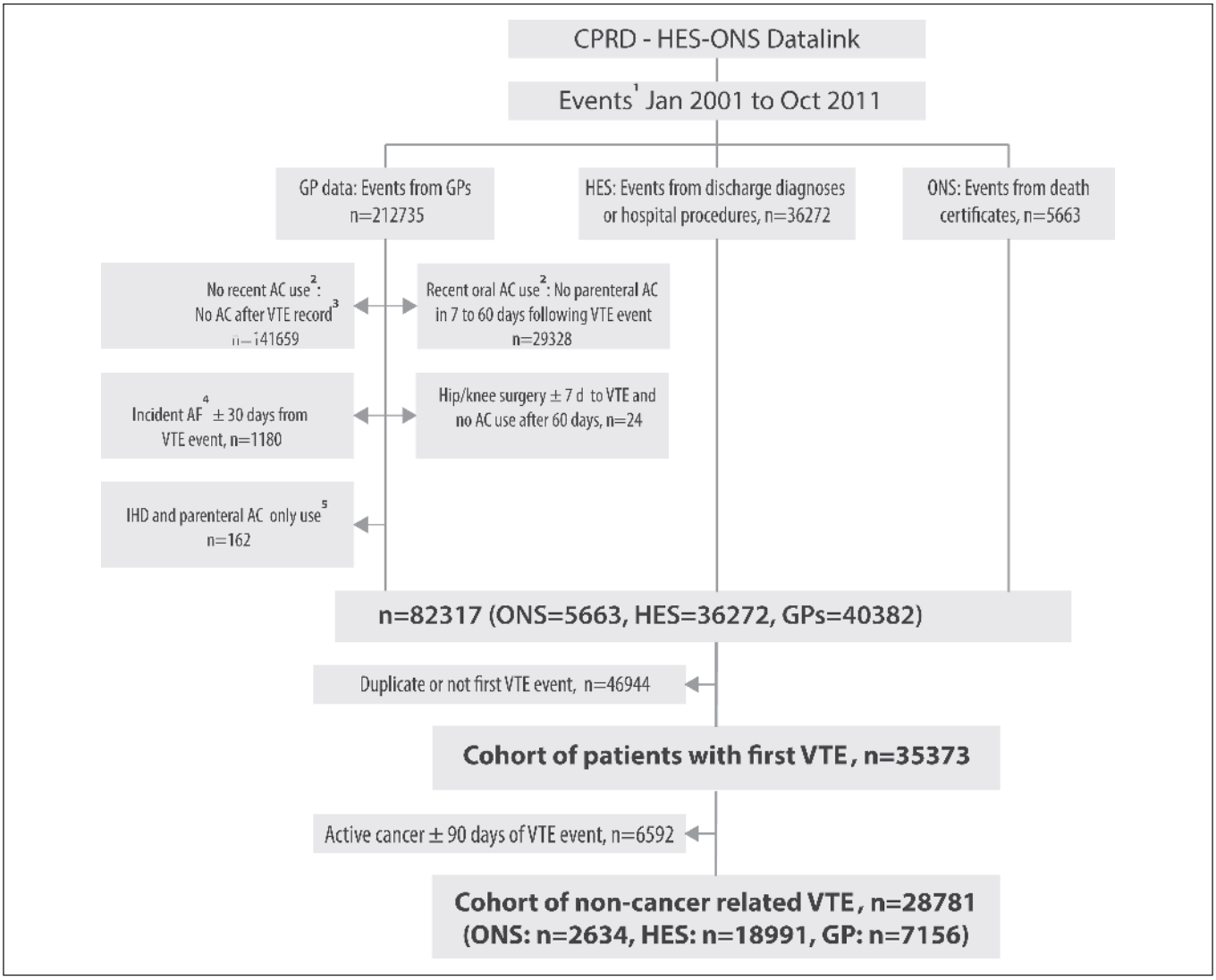


**Figure 1: Ascertainment of first VTE.** AC: anticoagulants; AF: atrial fibrillation; CPRD: Clinical Practice Research Datalink; GP: general practitioner; HES: Hospital Episodes Statistics IHD: ischaemic heart disease; ONS: Office for National Statistics Mortality data; VTE: venous thromboembolism. [1]Excludes events after patient transferred out of GP practice or without 365 day history before VTE record; [2]Vitamin K antagonists (VKA) use or ≥ 3 INR-tests 31–180 days prior to VTE; [3]Commencement of AC use: VKA or ≥ 3 INR-tests within –7 to 60 days of VTE, or ≥ 2 low-molecular-weight heparin (LMWH) prescriptions within 7 to 60 days after VTE; [4]AF, mechanical heart valves or left ventricular thrombosis; [5]Parenteral AC only use within –30 to 60 days after VTE.

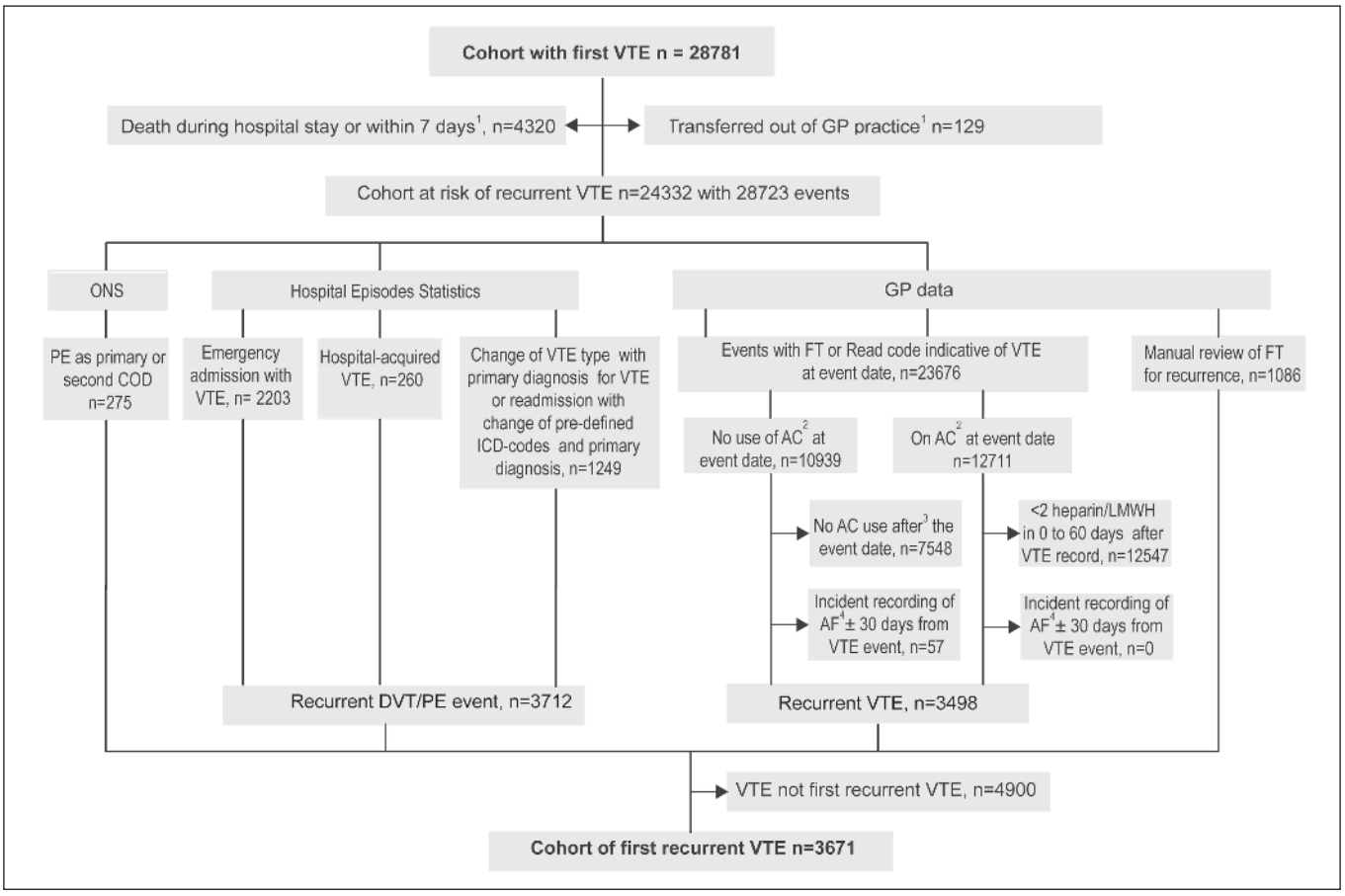


**Figure 2: Ascertainment of recurrent VTE.** AC: anticoagulants; AF: atrial fibrillation; COD: cause of death; DVT: deep-vein thrombosis; FT: free text notes; GP: general practitioner; HES: Hospital Episodes Statistics; LMWH: low-molecular-weight heparins. [1] During hospitalisation (HES) or within 7 days from date of first VTE (FT, CPRD); [2] AC defined as prior AC use or ≥2 INR-tests within 60 days before VTE. Patients with confirmed VTE are assumed to be on AC for 90 days; [3] Commencement of AC use: VKA or ≥ 3 INR-tests within – 7 to 60 days of VTE, or ≥ 2 LMWH within 7 to 60 days after VTE; [4] AF, mechanical heart valves or left ventricular thrombosis.

our study if patients were hospitalised, or if not hospitalised then they were included only if anticoagulation was given following a GP-based diagnosis for DVT (▶Figure 1).

Validation of specific medical codes was undertaken in the ambulatory setting, hospital discharge diagnoses, causes of death, type and duration of anticoagulant use, with anonymised clinical notes, clinic letters and discharge summaries in the database including subsequent treatment with anticoagulants in primary care. The manual review of random samples of potential first VTE was used to develop an algorithm for study outcomes and was modified by an iterative approach. Finally, an objective testing of the algorithm was performed based on review of anonymised clinical and hospital discharge letters from the entire CPRD with a recording of VTE. The sensitivity of the algorithm for detecting VTE was 92.6% (126 of 136) and the specificity was 98.6% (143/145).

VTE events with a recording for active cancer, defined as an admission to hospital with a primary diagnosis of cancer (excluding non-melanoma skin cancer), radiation, chemotherapy or bone marrow transplantation, in the three months before or the three months after the first VTE were excluded. Patients with a history of VTE or evidence of previous venous thrombosis such as post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension were excluded from the study cohort.

VTE events were assigned to DVT or PE, and to provoked VTE if there was a hospitalisation, a surgical procedure, trauma, fracture, oestrogen and progestrogene use or pregnancy/puerperium in the three months prior to the VTE, or a past history of cancer (not included in the definition of active cancer above). The remaining VTE cases were regarded as unprovoked VTE (idiopathic) (5).

## Recurrence of VTE

The incident VTE cohort was followed for recurrent VTE events. An algorithm for the definition of recurrent VTE was developed and refined using all information available in CPRD, HES and ONS. CPRD information included the search for key words in electronic clinical notes and the manual review of all clinical notes which indicated recurrence or anticoagulant use. Patients hospitalised for recurrent DVT and PE were required to

**Table 1: Baseline characteristics of the 28,781 patients with provoked or unprovoked first VTE.**

| | Provoked VTE | Unprovoked VTE | DVT | PE | Complete cohort |
|---|---|---|---|---|---|
| No. of patients | 12073 (41.9) | 16708 (58.1) | 15575 (54.1) | 13206 (45.9) | 28781 (100.0) |
| Males | 4903 (40.6) | 7867 (47.1) | 7009 (45.0) | 5761 (43.6) | 12770 (44.4) |
| Mean age ± SD, years | 67.5 ± 17.8 | 64.0 ± 18.9 | 63.4 ± 19.0 | 68.0 ± 17.5 | 65.5 ± 18.5 |
| < 18 | 35 (0.3) | 55 (0.3) | 67 (0.4) | 23 (0.2) | 90 (0.3) |
| 18 to 29 | 449 (3.7) | 817 (4.9) | 838 (5.4) | 428 (3.2) | 1266 (4.4) |
| 30 to 39 | 690 (5.7) | 1374 (8.2) | 1402 (9.0) | 662 (5.0) | 2064 (7.2) |
| 40 to 49 | 840 (7.0) | 1703 (10.2) | 1504 (9.7) | 1039 (7.9) | 2543 (8.8) |
| 50 to 59 | 1355 (11.2) | 2214 (13.3) | 2069 (13.3) | 1500 (11.4) | 3569 (12.4) |
| 60 to 69 | 2220 (18.4) | 2864 (17.1) | 2725 (17.5) | 2359 (17.9) | 5084 (17.7) |
| 70 to 79 | 2952 (24.5) | 3654 (21.9) | 3368 (21.6) | 3238 (24.5) | 6606 (23.0) |
| 80 to 89 | 2814 (23.3) | 3166 (18.9) | 2899 (18.6) | 3081 (23.3) | 5980 (20.8) |
| ≥ 90 | 718 (5.9) | 861 (5.2) | 703 (4.5) | 876 (6.6) | 1579 (5.5) |
| BMI | | | | | |
| Mean BMI± SD | 27.7 ± 6.0 | 28.1 ± 6.6 | 27.9 ± 6.1 | 28.1 ± 6.7 | 28.0 ± 6.3 |
| Missing BMI | 1886 (15.6) | 3040 (18.2) | 2659 (17.1) | 2267 (17.2) | 4926 (17.1) |
| Smoking status | | | | | |
| Known | 11380 (94.3) | 15527 (92.9) | 14538 (93.3) | 12369 (93.7) | 26907 (93.5) |
| Never | 5941 (52.2) | 8221 (52.9) | 7627 (52.5) | 6535 (52.8) | 14162 (52.6) |
| Ex-smoker | 3484 (30.6) | 4156 (26.8) | 3930 (27.0) | 3710 (30.0) | 7640 (28.4) |
| Current smoker | 1955 (17.2) | 3150 (20.3) | 2981 (20.5) | 2124 (17.2) | 5105 (19.0) |
| Missing smoking | 693 (5.7) | 1181 (7.1) | 1037 (6.7) | 837 (6.3) | 1874 (6.5) |
| Alcohol status | | | | | |
| Known | 10202 (84.5) | 13710 (82.1) | 12921 (83.0) | 10991 (83.2) | 23912 (83.1) |
| Never | 2328 (22.8) | 2878 (21.0) | 2673 (20.7) | 2533 (23.0) | 5206 (21.8) |
| Ex drinker | 355 (3.5) | 428 (3.1) | 416 (3.2) | 367 (3.3) | 783 (3.3) |
| Current drinker | 7519 (73.7) | 10404 (75.9) | 9832 (76.1) | 8091 (73.6) | 17923 (75.0) |
| Missing alcohol | 1871 (15.5) | 2998 (17.9) | 2654 (17.0) | 2215 (16.8) | 4869 (16.9) |
| Socioeconomic status | | | | | |
| Known | 7212 (59.7) | 9971 (59.7) | 9475 (60.8) | 7708 (58.4) | 17183 (59.7) |
| 1st quintile (least deprived) | 1699 (23.6) | 2549 (25.6) | 2342 (24.7) | 1906 (24.7) | 4248 (24.7) |
| 2nd quintile | 1590 (22.0) | 2153 (21.6) | 2059 (21.7) | 1684 (21.8) | 3743 (21.8) |
| 3rd quintile | 1517 (21.0) | 1982 (19.9) | 1933 (20.4) | 1566 (20.3) | 3499 (20.4) |
| 4th quintile | 1382 (19.2) | 1888 (18.9) | 1812 (19.1) | 1458 (18.9) | 3270 (19.0) |
| 5th quintile | 1024 (14.2) | 1399 (14.0) | 1329 (14.0) | 1094 (14.2) | 2423 (14.1) |
| Missing socioeconomic status | 4861 (40.3) | 6737 (40.3) | 6100 (39.2) | 5498 (41.6) | 11598 (40.3) |
| DVT, n (%) | 6309 (52.3) | 9266 (55.5) | 15575 (100.0) | 0 (0.0) | 15575 (54.1) |
| PE, n (%) | 5764 (47.7) | 7442 (44.5) | 0 (0.0) | 13206 (100.0) | 13206 (45.9) |
| DVT/PE ratio | 1.1 | 1.2 | - | - | 1.2 |

n (%) unless otherwise indicated; VTE: venous thromboembolism; DVT: deep-vein thrombosis; PE: pulmonary embolism.

have an emergency type of admission or to have an explicit mentioning of a "recurrent VTE" in the patient's anonymized medical notes. The algorithm for recurrent VTE was developed and modified by an iterative approach as described above for the first VTE events (▶Figure 2). To objectively validate the algorithm for recurrent VTE we identified a total of 378 patients with clinical letters and hospital discharge summaries from the pool of patients with first VTE. The anonymised letters were reviewed and classified as recurrent or not recurrent VTE. The algorithm yielded a sensitivity of 79.19% (118/149) and a specificity of 97.23% (223/229).

### Data analysis

Descriptive statistics were conducted to present the demographic characteristics in the provoked, unprovoked, DVT and PE cohorts. Continuous variables were presented as mean and standard deviation (SD). Categorical variables were presented as counts and percentages. Crude incidence rates of VTE were calculated from the number of new observed outcome events and the sum of individual person-years contributed by the CPRD/HES/ONS population during the study period. Crude incidence rates of recurrent VTEs were derived from the number of confirmed new recurrent events and the person-years contributed by the population with first VTE. Simple Kaplan-Meier curves assume censoring is non-informative, such that the risk of a study outcome is similar in patients remaining alive and those censored at the time of death. As this assumption may not be met, survival rates were derived using competing risk models. The probability of failure for VTE recurrence is presented as the cumulative incidence rates (CIR) at a given point in time and derived from a cumulative incidence estimator accounting for mortality as a competing risk event (11). The cumulative risk estimate corresponds to the probability of occurrence of VTE recurrence and does not imply a cause-specific probability. Thus the probability of VTE recurrence could have been modified by the occurrence of a complication of the first VTE.

All statistical procedures were performed using the STATA MP Version 12.1 (StataCorp LP).

The study protocol was approved by the Independent Scientific Advisory Committee for CPRD research.

## Results

### Incident VTE

A total of 35,373 first VTE events were identified among 26.9 million person-years of observation between 2001 and 2011 (▶Figure 1). Of the total VTEs 6592 (18.6%) were active-cancer-associated, 12,073 (34.1%) had a common risk factor (provoked), and 16,708 (47.2%) assigned as unprovoked VTE. The overall incidence rate of first VTE was 131.5 (95% confidence interval [CI], 130.2–132.9) per 100,000 person-years and for the 28,781 non-cancer associated VTE events 107.0 (95% CI, 105.8–108.2). Of the non-cancer associated VTEs 15,575 (54.1%) were DVT, 13,206 (45.9%) PE with or without DVT.

The mean age was 65.5 years, 67.5 for provoked VTE and 64.0 for unprovoked VTE. Patients with first DVT were younger than those with first PE, 63.4 vs 68.0 years. DVT was much commoner than PE in the young with 14.8% of DVT cases occurring in those less than 40 compared to 8.4% of PE cases. VTE was more common among women (55.6%). The DVT to PE ratio was 1.1 in provoked VTE and 1.2 in unprovoked VTE (▶Table 1).

The incidence rate increased with age independently of gender and was significantly increased in women with 117.9 (95% CI, 116.0–119.7) per 100,000 person-years compared to 95.9 (95% CI,

**Table 2: Incidence rates per 100 person-years with 95% confidence intervals of recurrent VTE by VTE type and VTE group (provoked and unprovoked).**

| | Recurrent VTE IR (95% CI) | Subset of patients with first PE | Subset of patients with first DVT | Provoked VTE | Unprovoked VTE |
|---|---|---|---|---|---|
| < 180 days | 11.1 (10.5–11.8) | 11.4 (10.4–12.5) | 10.9 (10.1–11.8) | 10.0 (9.0–11.0) | 11.9 (11.0–12.8) |
| 181 – 365 days | 8.1 (7.6–8.7) | 9.4 (8.4–10.4) | 7.4 (6.7–8.1) | 6.3 (5.5–7.1) | 9.4 (8.6–10.3) |
| 1 to <2 years | 4.6 (4.3–5.0) | 4.7 (4.1–5.3) | 4.6 (4.2–5.1) | 3.3 (2.8–3.8) | 5.6 (5.1–6.1) |
| 2 to <3 years | 3.2 (2.9–3.5) | 3.3 (2.8–3.9) | 3.1 (2.7–3.5) | 2.3 (1.9–2.8) | 3.8 (3.3–4.3) |
| 3 to <4 years | 2.9 (2.5–3.2) | 2.8 (2.2–3.4) | 2.9 (2.5–3.4) | 2.0 (1.6–2.5) | 3.5 (3.0–4.0) |
| 4 to < 5 years | 2.6 (2.2–3.0) | 2.5 (1.9–3.2) | 2.6 (2.2–3.2) | 2.1 (1.6–2.7) | 3.0 (2.5–3.5) |
| 5 to < 6 years | 2.1 (1.7–2.5) | 2.1 (1.5–2.9) | 2.1 (1.6–2.6) | 2.0 (1.5–2.7) | 2.1 (1.7–2.7) |
| 6 to <7 years | 2.2 (1.8–2.8) | 2.3 (1.6–3.3) | 2.2 (1.6–2.9) | 1.7 (1.1–2.4) | 2.7 (2.0–3.5) |
| 7 to <8 years | 2.4 (1.8–3.0) | 2.5 (1.6–3.8) | 2.2 (1.6–3.1) | 2.2 (1.4–3.3) | 2.4 (1.7–3.4) |
| 8 to <9 years | 1.6 (1.0–2.3) | 1.2 (0.5–2.4) | 1.8 (1.1–2.9) | 0.9 (0.3–2.0) | 2.0 (1.2–3.2) |
| 9 to <10 years | 1.4 (0.7–2.6) | 2.0 (0.7–4.4) | 1.1 (0.3–2.5) | 1.8 (0.7–4.0) | 1.1 (0.4–2.6) |
| Complete observational period | 4.9 (4.7–5.0) | 5.1 (4.8–5.4) | 4.7 (4.5–4.9) | 3.8 (3.6–4.1) | 5.6 (5.4–5.8) |

IR: incidence rate; VTE: venous thromboembolism; DVT: deep-vein thrombosis; PE: pulmonary embolism.

94.3–97.6) per 100,000 person-years in men (►Figure 3 and Suppl. Table 1, available online at www.thrombosis-online.com).

The breakdown by ethnic origin showed a crude incidence rate of VTE among whites of 151.1 per 100,000 person-years, 94.7 for blacks and 69.4 for Asians. When standardised by age, Asians appear to have the lowest incidence rate of first VTE with 121.7 per 100,000 person-years while white and blacks had rates of 190.8 and 203.0, respectively (Suppl. Table 2, available online at www.thrombosis-online.com).

## Recurrent VTE

Of the 28,781 patients with non-active cancer associated VTE, 4320 died, and 129 were censored for leaving their practice, the remaining 24,332 patients were at risk of recurrent VTE. Of those, 3671 cases of recurrent VTE were identified in a total of 75,548 person-years of observation (►Figure 2) yielding an incidence rate of recurrence of 4.9 (95% CI, 4.7 – 5.0) per 100 person-years, with 4.7 per 100 person-years following first DVT and 5.1 per 100 person-years following first PE. The VTE recurrence rate peaked in the 180 days following the first VTE event at 11.1 per 100 person-years and plateaued between four and 10 years at approximately 2.2 per 100 person-years (►Table 2 and ►Figure 4).

Over 10 years the crude cumulative risk of recurrent VTE was 25.2%, and did not depend on the type of the first VTE, i.e. DVT or PE, but was significantly lower among provoked VTE compared to unprovoked VTE, 20.5% and 28.4%, respectively (p<0.001) (►Figure 5).

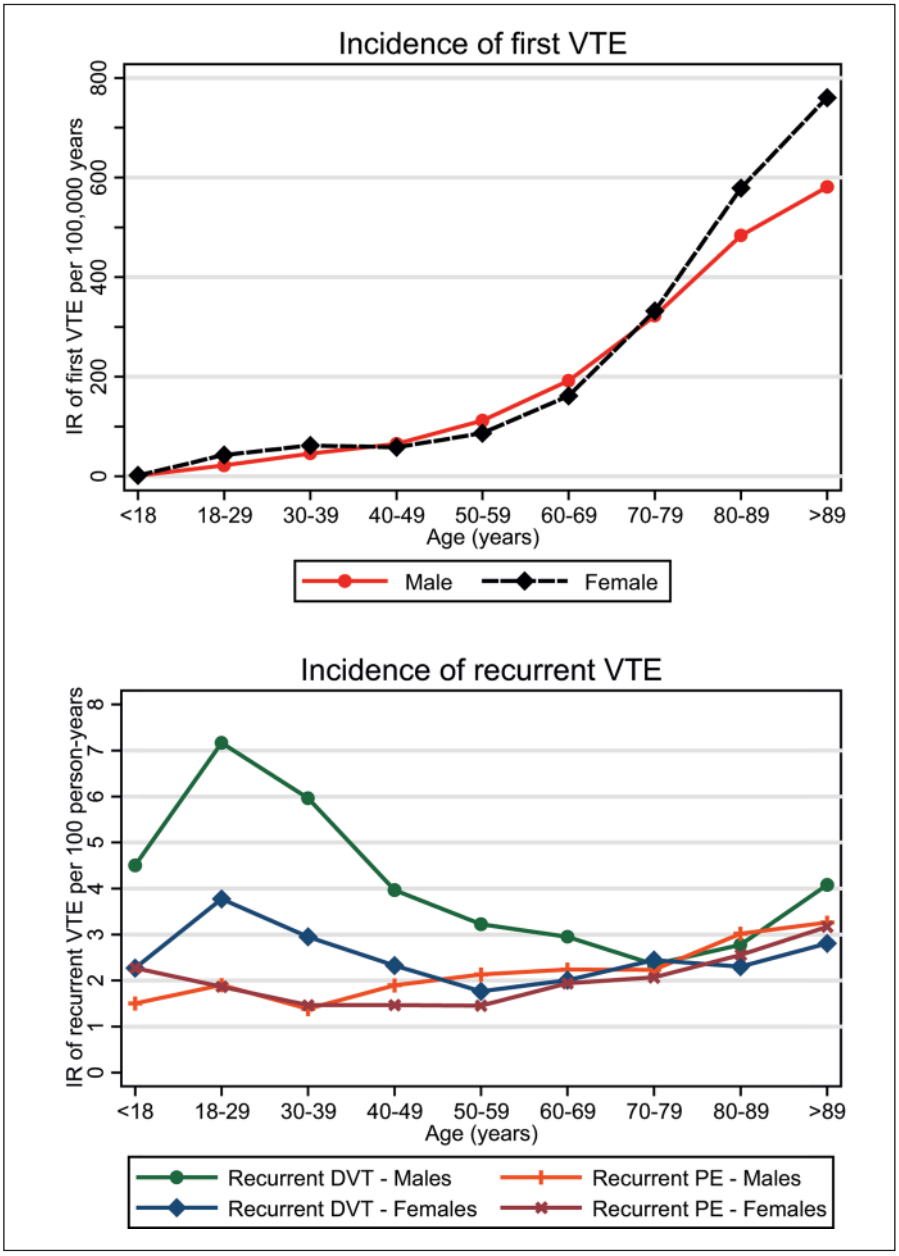


**Figure 3: Age- and gender-specific incidence rates of first VTE per 100,000 population per year (upper panel) and of recurrent VTE per 100 patients with first VTE per year (lower panel).**

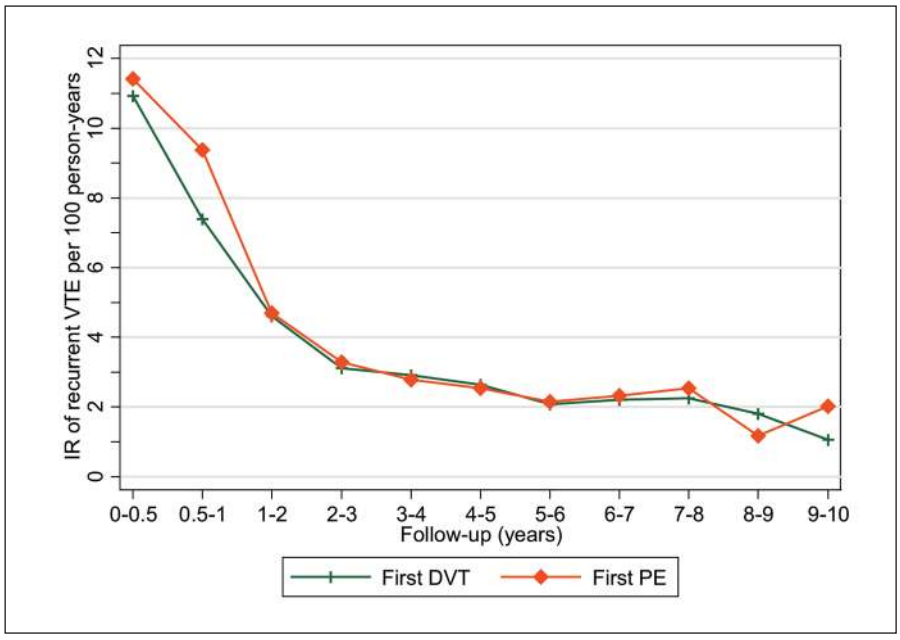


**Figure 4: Incidence rates of recurrent VTE per 100 person-years and time since first VTE following first DVT and first PE.**

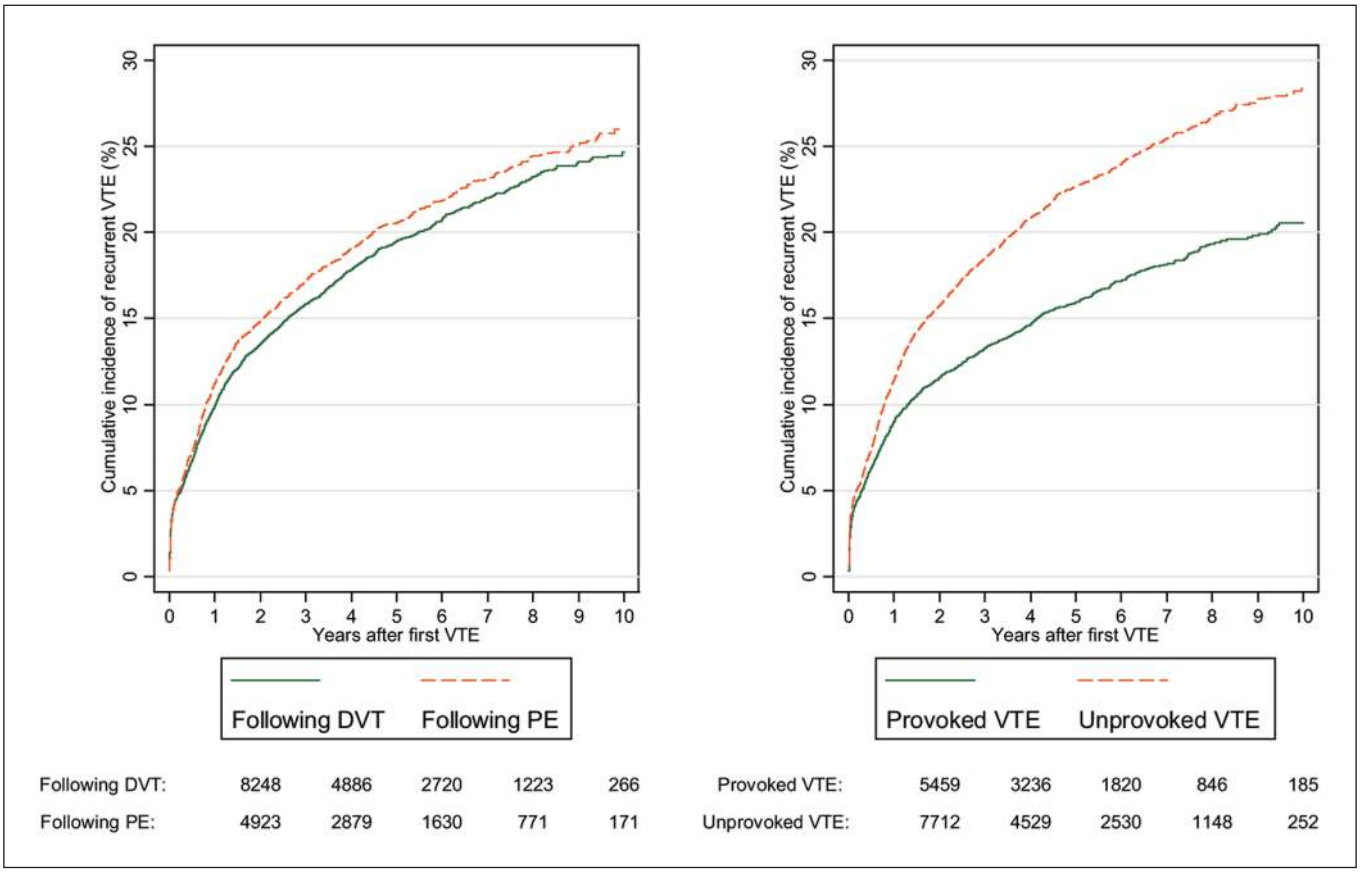


**Figure 5: Crude cumulative incidence of recurrent VTE by initial presentation as DVT or as PE, and by provoked or unprovoked VTE.**

Incidence rates for VTE recurrences following a first DVT were highest in the younger population, particularly young males (►Figure 3 and Suppl. Table 3, available online at www.thrombosis-online.com).

### All-cause mortality

The mortality risk following VTE derived from Kaplan-Meier estimates was considerable with 21.6% mortality after one year, 25.5 after two years, 28.9 after three years, 34.5 after five years and 47.1% in 10 years.

## Discussion

This very large VTE cohort had a follow up to 10 years that allowed us to accurately describe the epidemiology of VTE and subsequent recurrences in much detail in the broad population. The incidence rate of non-cancer associated VTE was 107.0 per 100,000 per year (95% CI, 105.8–108.2), with rates of 95.9 (95% CI, 94.3–97.6) in men and 117.9 (95% CI, 116.0–119.7) in women. The higher rates in women were due to higher rates in women aged less than 50 and over 70. In contrast to some studies we found that the majority of cases of VTE were unprovoked (58.1%). Patients in chronic care facilities may account for 13–15% of VTE cases, and we did not assess these patients as having "provoked disease" (12).

### What is known about this topic?

- Venous thromboembolism (VTE) is a prevalent condition with an incidence rate in patients without active cancer of around 100 per 100,000 per year.
- Data on the epidemiology of first VTE and recurrences are limited, rarely assessing the demographics and associations in detail
- The complication of recurrence has been described in cohorts of relatively few patients.

### What does this paper add?

- Data on a very large current cohort that describes in detail the epidemiology of first and recurrent VTE in the broad population involving patients diagnosed in primary care, secondary care and at death.
- The finding that the incidence of recurrent VTE, in particular DVT, peaks at age 18 to 29, highest in males, and remains elevated until the age of 40.
- A precise description of first VTE and of the incidence rates for recurrences overall (with a peak at 11.1 per 100 person-years in the first six months, falling to 8.1 between 6–12 months and to 4.6 in 1 to 2 years.) and for the major subgroups of this condition: deep-vein thrombosis, pulmonary embolism, provoked and unprovoked VTE.

### Recurrences

The overall incidence rate for recurrent VTE was 4.9 per 100 person-years with a peak at 11.1 per 100 person-years in the first six months, falling to 8.1 between 6–12 months. These findings support current guidelines for at least three months anticoagulation therapy and suggest that longer periods may be required (7). Consistent with other studies, overall crude recurrence rates were higher in males (►Figure 3) (13). Recurrence was not influenced by whether the index event was a DVT or PE. Recurrence in the first 10 years of observation was higher in unprovoked cases as previously described (►Figure 5) (7). Patients with unprovoked VTE have high rates of recurrence, suggesting unrecognised persisting VTE risk factors (14).The cumulative frequencies of recurrences at six and 12 months (7.0% and 10.5%) were consistent with previous publications with around 4%-8.6% at six months and 5%-15% at 12 months (7, 15). Despite current management, our estimates are much higher than the figures for clinical trials (1–2% and 2–3%, respectively) possibly due to the exclusion of higher risk patients, and the possible underutilisation of anticoagulants in real life.

Our observation that the incidence rates for recurrence of DVT were higher in younger patients (►Figure 3) raises the possibility that young patients presenting with first VTE have a more potent prothrombotic state which also drives higher rates of recurrence.

### Strengths

Our study was designed to collect information during a 10-year observational period on first and recurrence of VTEs, including children and the very elderly. It demonstrates the importance of using hospital and death data to overcome incomplete recording when using one source only, such as primary care data (16). Previous studies using either hospital databases or primary care data would have underestimated the incidence rate of VTE by not having access to a large proportion of both fatal or hospital cases not reported to primary care. We were able to find an extra 45% of cases by examining hospital and mortality data, and medical notes in addition to coded primary care records. Our validation process was thorough for both incident and recurrent events.

Reviewing disorder-specific data for first and recurrent VTEs required defining all the separate components which needed amalgamating. Some true cases may have not been identified by discarding non-specific or incompletely recorded cases. Additional use of medical notes, hospital and death certificate data considerably increased the sensitivity of detecting VTE. Also, the required use of anticoagulants for GP-identified cases of first and recurrent VTE increased the specificity of case identification (10).

### Limitations

The information in each database has its inherent weaknesses. HES has varied coding accuracy and we were careful to remove all non-specific ICD codes. CPRD data required special attention and cycles of testing and validation. ONS use death certificate data and

 

greatly underestimate the frequency of VTE related deaths due to difficulty in diagnosis. Most autopsy series show that PE is the cause of death in 5–15% of patients, with a figure of around 10% most commonly reported (17). Fatal PE is underestimated, with these studies showing around only one third to one half being diagnosed ante mortem (17, 18).

Our definition of provoked VTE was heavily based on hospitalisations for a medical illness or a surgical procedure. Patients with a thrombotic episode following disease not leading to hospitalisation, e.g. care home, prolonged immobilization following a fracture, travel or other causes are not recorded, and would have been misclassified as having idiopathic VTE and resulting in overestimation of VTE labelled as unprovoked.

Data on inpatient drug use, medications dispensed at hospital discharge and anticoagulation clinic prescriptions were limited or not available in our study. As our algorithms for detection of first and recurrent VTEs were partly based on anticoagulant use, incidence rates for non-hospitalised VTE cases treated in hospital outpatient clinics are likely to be underestimated. The distinction between distal and proximal events was not possible as the location of the DVT was only recorded infrequently. As distal DVT may not be treated with anticoagulants some cases will have been missed. Despite these limitations our study demonstrated similar incidence rates for DVT, PE and recurrences to other population studies (3, 19), but with more precision and more detail on many factors such as demographics, social class, break down by age, subgroups and aetiology.

## Conclusions

VTE is a relatively common disorder associated with frequent recurrences despite current management. VTE is often provoked and follows a recognised event (41.9%). Efforts are needed to prevent VTE and to reduce complications such as recurrences.

### Conflicts of interest

This work was supported by Bayer Pharma AG, Germany. The financial sponsor contributed to the conception of the study but did not play a role in the design, execution, analysis, interpretation of data, or writing of the manuscript.

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