Venous thromboembolism (VTE) in Europe

The number of VTE events and associated morbidity and mortality

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Summary

Venous thromboembolism (VTE) is often asymptomatic, misdiagnosed, and unrecognized at death, and there is a lack of routine postmortem examinations. These factors are thought to result in marked underestimates of VTE incidence. The objective of our study was to estimate the total burden of VTE within the European Union (EU) per annum. An epidemiological model was constructed to estimate the number of community- and hospital-acquired incidents and recurrent cases (attack rate) of non-fatal VTE and VTE-related deaths, as well as incident and prevalent cases of post-thrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension (PH) occurring in the EU per annum. Individual models were developed for six EU countries. The models were populated with data from published literature and, where necessary, expert opinions. The findings were tested using probabilistic sensitivity analyses. The estimated total number of symptomatic VTE events (range based on probabilistic sensitivity analysis) per annum within the six EU countries was 465,715 (404,664–538,189) cases of deep-vein thrombosis, 295,982 (242,450–360,363) cases of pulmonary embolism (PE), and 370,012 (300,193–483,108) VTE-related deaths. Of these deaths, an estimated 27,473 (7%) were diagnosed as being antemortem; 126,145 (34%) were sudden fatal PE, and 217,394 (59%) followed undiagnosed PE. Almost three-quarters of all VTE-related deaths were from hospital-acquired VTE. VTE is a major health problem in the EU, with over one million VTE events or deaths per annum in the six countries examined. Given the availability of effective VTE prophylaxis, many of these events and deaths could have been prevented. These results have important implications for the allocation of healthcare resources.

Keywords

Deep-vein thrombosis, post-thrombotic syndrome, pulmonary embolism, pulmonary hypertension, venous thromboembolism, VTE prophylaxis

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Introduction

Venous thromboembolism (VTE), comprising deep-vein thrombosis (DVT) and pulmonary embolism (PE), is associated with substantial morbidity and mortality. Detailed estimates of the annual number of VTE events are hard to obtain because VTE is difficult to diagnose. This is due to a number of factors; VTE is often clinically silent and, in many cases, the first sign of the disease is a sudden fatal PE (1, 2). Despite modest increases in antemortem diagnosis of PE over the years, less than half of autopsy-detected PE cases are diagnosed antemortem (3). The lack of routinely performed postmortem examinations means that many

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fatal pulmonary emboli remain unrecognized, leading to an underestimation of their incidence. Previous analyses have shown that, for every case of symptomatic non-fatal PE, there are 2.5 cases of fatal autopsy-detected PE (4). Only 29% of patients who survive an initial embolic event are diagnosed with VTE (5). In 36% of patients diagnosed with PE, an initial diagnosis is made on the date of death or postmortem, with PE being the cause of death in 53% of these cases (2). Studies have also shown that asymptomatic DVT is strongly associated with the development of symptomatic VTE (6–8) and is also associated with an increased risk of death (9). Due to these factors, modeling is the only approach to achieve annual incidence figures and estimates of complications.

The chronic nature of VTE and its recurrences and complications requires considerable healthcare resources for its management. Additionally, morbidity and healthcare costs are incurred from associated complications of VTE, such as post-thrombotic syndrome (PTS), which affects at least one-third of DVT patients (10–17), and pulmonary hypertension (PH), which occurs in 4%–5% of patients following PE (18, 19). Data from the UK suggest that the total cost of VTE to the National Health Service in 1993 was £235–£257 million (€349–€382 million) (20), and estimates of the combined direct and indirect costs are now placed at approximately £640 million (€950 million) (21). The costs are further increased when long-term complications such as PTS are taken into consideration (22, 23). Therefore, it is important for healthcare decision-makers to have reliable estimates of the total annual number of incident and recurrent VTE events per year.

To date, the most comprehensive epidemiological data have been generated from studies of specific populations. US population-based studies of defined geographical areas, which included patients with only incident VTE at home or in hospital, revealed a VTE incidence of 71–117 per 100,000 person-years (24–26). One study also showed a thirty-day rate of VTE recurrence of 4.8% (26). In Europe, studies in Western France (27)

Table 1: Sources of data.

Event estimated	Source of data	Probability (range) of event
Community-acquired events		
Age and gender specific	Oger 2000 (27)	-
Country-specific population data	US Census Bureau International Data base (28)	-
Hospital-acquired events		
At-risk populations	HES (29) and PMSI (30) databases	-
Surgical risk group		
DVT and PE without prophylaxis	Geerts et al. 2004 (31)	-
DVT and PE with prophylaxis	Derived from Geerts et al. 2004 (31)	-
Medical risk group		
DVT with and without prophylaxis	Geerts et al. 2001 (32)	-
PE with and without prophylaxis	Derived from Geerts et al. 2001 (32)	-
PTS		
Mild/moderate PTS in patient with DVT	Derived from Prandoni et al. 1996 (10)	0.147 (0.074–0.221) first year, 0.01 (0.005–0.015) in following years
Severe PTS in patient with DVT (new)	Prandoni et al. 1996 (10)	0.026 (0.013–0.039) first year, 0.017 (0.009–0.026) in following years
PH	Pengo et al. 2004 (18)	0.31 (0.16–0.47) first year, 0.38 (0.19–0.57) in following years
DVT		
Symptomatic and diagnosed	Geerts et al. 2004 (31); Piovella et al. 2005 (35)	0.10 (0.05–0.15)
Death from DVT	Oster et al. 1987 (33)	0.006 (0.003–0.009)
Medical DVT that has developed into PE	Oster et al. 1987 (33)	0.115 (0.058–0.173)
PE		
Symptomatic and diagnosed	Oster et al. 1987 (33)	0.29 (0.15–0.44)
Sudden death from PE	Oster et al. 1987 (33)	0.11 (0.06–0.17)
Death from undiagnosed PE	Oster et al. 1987 (33)	0.30 (0.15–0.45)
Death from diagnosed PE	Oster et al. 1987 (33)	0.08 (0.04–0.12)
DVT recurrence	Prandoni et al. 1996 (10); Heit et al. 2000 (34)	0.104 (0.052– 0.156) first year, 0.02 (0.01–0.03) in following years
PE recurrence	Prandoni et al. 1996 (10); Heit et al. 2000 (34)	0.025 (0.013–0.038) first year, 0.005 (0.003–0.008) in following years

DVT, deep-vein thrombosis; HES, Hospital Episodes Statistics; PE, pulmonary embolism; PH, pulmonary hypertension; PMSI, Le Programme de Médicalisation des Systèmes d'Information; PTS, post-thrombotic syndrome.

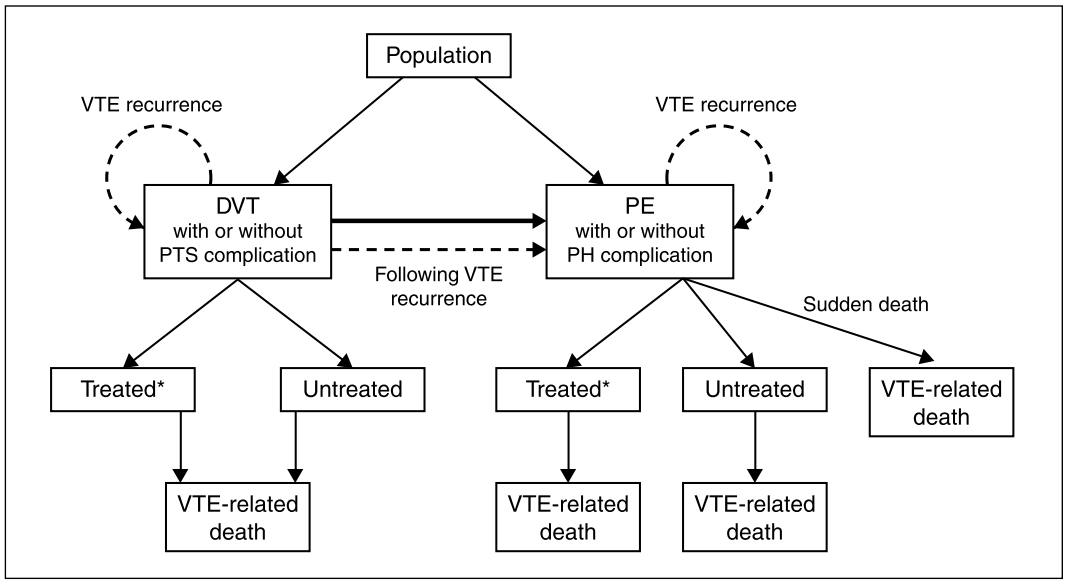

Figure 1: General model structure for estimating the number of country-specific, non-fatal symptomatic venous thromboembolism (VTE) events and VTE-related deaths in a one-year period. *Treated deep-vein thrombosis (DVT) and pulmonary embolism (PE) (for the purpose of the model, we assume all diagnosed VTE is treated). PH, pulmonary hypertension; PTS, post-thrombotic syndrome.

and Sweden (5), that included both incident and recurrent VTE events, reported an overall VTE incidence of 160–180 per 100,000 person-years. Although these studies have contributed considerably to our understanding of the epidemiology of VTE, they underestimate the total burden of the disease on the healthcare system because they do not include undiagnosed or misdiagnosed clinical VTE events or unrecognized VTE-related deaths.

In view of the potential impact of VTE to public health and the lack of comprehensive estimates on the number of symptomatic VTE events and associated morbidity and mortality in Europe, the VTE Impact Assessment Group in Europe (VITAE) designed a modified incidence-based model to estimate the total annual number of non-fatal incident and recurrent VTE events, associated complications (PTS and PH), and VTE-related deaths in six countries within the European Union (EU).

Methods

Data searches

An extensive search of national databases was performed looking at published papers and grey literature. The search was conducted using MEDLINE and EMBASE databases between 1994 to date. Seventy-five original papers were identified that described new epidemiological research. Only those giving information about the prevalence and incidence in Europe in defined geographical populations were used in the model. Key search terms were "venous thromboembolism", "deep-vein thrombosis", and "pulmonary embolism". These terms were crossed with the terms "epidemiology", "prevalence", "incidence", "risk factors", and "natural history".

Model structure

A model was developed to estimate the number of country-specific, non-fatal symptomatic VTE events and VTE-related deaths in a one-year period. Events estimated included incident and recurrent cases of non-fatal VTE, and incident and existing cases of PTS, PH, and VTE-related death. The base year for estimating events was 2004.

The core model structure, methodologies, and assumptions were validated by an advisory board consisting of VTE experts from across Europe and the USA. Individual models were developed for six EU countries: France, Germany, Italy, Spain, Sweden, and the UK. Wherever possible, the parameter estimates for models were derived from data in the published literature (Table 1) (10, 18, 27–35). Where data on model parameters were unavailable, the advisory board provided an expert opinion on the plausible ranges for sensitivity analyses. Published data were used as a source for all event rates, for the at-risk hospital population, and for the probabilities of events. Estimates of prophylaxis rates from experts in the individual countries were only used when published data were not available. Where there were any differences, or disagreements arose, experts were asked to reach a consensus.

The model estimated the number of community-acquired VTE events and hospital-acquired VTE events. Hospital-acquired events were defined as events that occurred following exposure to hospital-related risk factors, surgical procedures, or admission to a medical ward, and which occurred within a hospital setting or in the community within a 90-day period of admission to hospital. Events not meeting these criteria were classified as community-acquired. The general model structure applies to both community- and hospital-acquired events (Fig. 1).

Estimation of the number of community-acquired events

Community-acquired events for each of the six EU countries were estimated on the basis of a large French epidemiological study (the Groupe d'Etude de la Thrombose de Bretagne Occidentale [EPI-GETBO] study) (27) with age- and gender-specific incidence rates applied to country-specific population data. The authors of the EPI-GETBO study (27) re-analyzed their study and provided additional data. They separated the events that took place in the community occurring within three months of hospi-

Table 2: At-risk hospital population estimates (baseline) extracted from or based on the Hospital Episodes Statistics (29) and Le Programme de Médicalisation des Systèmes d'Information (30) databases 2004.

	France	Germany	Italy	Spain	Sweden	UK
General population	60,424,000	82,425,000	58,058,000	40,281,000	8,986,000	60,271,000
At-risk population						
Surgical						
Moderate risk	577,362	751,436	532,200	385,328	84,178	599,355
High risk	1,155,368	1,487,275	1,035,322	660,542	153,689	742,324
Highest risk	365,212	474,948	339,129	216,299	50,576	250,162
Medical						
Myocardial infarction*	15,250	25,883	18,685	11,930	2,795	18,651
Stroke	67,499	106,691	79,025	50,464	11,876	74,678
Other medical†	1,130,796	1,416,345	1,019,501	651,004	152,406	720,880

†Cardiac, respiratory, and inflammatory diseases and severe infections. *The majority of patients with myocardial infarction receive anticoagulant therapy and are excluded.

talization (16% of these events). As in the VITAE study these would not constitute a community-acquired event. The re-analysis of the EPI-GETBO study (27) also allowed the calculation of age-adjusted numbers of events for community-acquired VTE.

Estimation of the number of hospital-acquired events

Patients were included in the hospital-acquired events model if they were deemed to be at risk of developing VTE (the at-risk population), and met the aforementioned criteria. At-risk populations were estimated on the basis of patient numbers derived from the Hospital Episodes Statistics (HES) database (29) in the UK and Le Programme de Médicalisation des Systèmes d'Information (PMSI) database (30) in France (Table 2). All HES and PMSI diagnostic and procedure codes relating to disease groups were carefully reviewed and those deemed to put a patient at risk of VTE according to current American College of Chest Physicians (ACCP) consensus guideline definitions (31) were included. At-risk patients from both public and private sectors were included. The hospital at-risk population was then divided into categories according to either type of surgery (moderate, high, and highest risk of VTE), or medical diagnosis on admission (myocardial infarction, stroke, and other medical diagnoses associated with VTE risk, e.g. heart failure, respiratory failure, infectious and inflammatory diseases) (36). Cancer patients were not separately included in order to avoid double counting with cancer leading to surgery. This is because coding does not specify whether an admission for cancer leads to operation or whether an operation, such as colectomy, is for a benign or malignant condition. We also did not include hematological cancers such as leukemia, and other cancers not known to be associated with VTE (e.g. skin cancers). Hence we took a conservative approach. In addition, patients who were in hospital for day procedures and minor surgery were excluded. Diagnoses requiring therapy with anticoagulants were also excluded.

The at-risk populations for the UK and France were based on the HES (29) and PMSI (30) data, respectively. These databases are robust and readily accessible sources of patient-level data. Equivalent databases were either not available, or the method of data collection was inconsistent with HES and PMSI for the other countries. For these countries (Germany, Italy, Spain, and Sweden), a weighted average of the UK and French data was used to derive patient numbers. For each at-risk group, the age-

Table 3: Probability of venous thromboembolism (VTE) events extracted or derived from Geerts et al. 2001 (32) and 2004 (31).

	Probability of VTE event			
	Without prophylaxis		With prophylaxis	
At-risk population	**DVT***	**PE†**	**DVT***	**PE†**
Surgical				
Moderate risk	0.150	0.052	0.041	0.027
High risk	0.300	0.103	0.081	0.054
Highest risk	0.600	0.241	0.162	0.126
Medical				
Myocardial infarction	0.240	0.025 (0.27)§	0.075	0.008
Stroke	0.547	0.057 (0.067)§	0.235	0.024
Other medical‡	0.160	0.017 (0.047)§	0.040	0.004

*Objectively verified by venography (i.e. all deep-vein thrombosis [DVT] events – both symptomatic and asymptomatic). †In order to calculate mortality, the frequency of pulmonary embolism (PE) for surgical patients was inflated from the probability of diagnosed clinical PE to the probability of all PE (i.e. to include undiagnosed clinical PE) (37). For medical patients, the PE frequency was calculated by applying the Oster algorithm (33) to DVT frequencies. ‡Cardiac, respiratory, and inflammatory diseases and severe infections. §Figures based on clinical trials and inflated from the probability of diagnosed clinical PE to the probability of all PE.

adjusted number of VTE events was calculated on the basis of the weighted data and this was applied to age-specific breakdowns of the relevant country populations.

Hospital-acquired events were estimated by applying specific risk frequencies for developing VTE to the surgical and medical at-risk populations, according to whether or not they were receiving VTE prophylaxis. The probability of developing VTE with and without prophylaxis (Table 3) (31–33, 37) was combined with estimates of current prophylaxis use (Table 4) in order to calculate the number of incident clinical VTE events in each at-risk group. Prophylaxis use was estimated based on published data wherever possible and, if otherwise, on expert consensus.

Estimation of the number of recurrent VTE events

In order to fully capture the number of VTE events expected in a given year, we estimated the number of recurrent clinically evident events alongside incident cases of clinical VTE. The majority of cases of recurrence occur within the first year of the index

At-risk population	France	Germany	Spain	Italy	Sweden	UK
Surgical						
Moderate risk	0.80	0.80	0.60	0.50	0.80	0.40
High risk	0.90	0.85	0.80	0.70	0.80	0.90
Highest risk	0.95	0.95	0.78	0.90	0.95	0.70
Medical						
Myocardial infarction	0.85	0.55	0.60	0.30	0.20	0.48
Stroke	0.85	0.85	0.60	0.20	0.20	0.48
Other medical*	0.60	0.62	0.62	0.25	0.20	0.30

*Cardiac, respiratory, and inflammatory diseases and severe infections.

Table 4: Probability (baseline estimate) of venous thromboembolism prophylaxis use in the at-risk population estimated from published data and clinician estimates, 2004.

event; however, the cumulative frequency continues to increase as time from the index event elapses (34). Total recurrent events expected in a given year therefore comprised recurrences of incident cases occurring in that year plus recurrences from incident events occurring in previous years. In order to incorporate this into the model, we assumed a constant incidence of index VTE over the previous five years and applied 1- to 5-year recurrence rates to these data (Table 5) (10, 18, 34).

Estimation of the numbers of PTS and PH events

A similar approach was taken to estimate the expected number of PTS cases. Total cases expected in a given year therefore comprised PTS related to incident cases of VTE occurring in that year plus PTS related to incident cases of VTE occurring in the previous five years (10). However, given that PTS is a chronic disease, there is also an underlying level of disease existing in any given year that is equivalent to the sum of cases developed in previous years. In the model, PTS was further separated into mild/moderate disease and severe disease. This distinction was made because disease severity drives resource use. We assumed that once a patient has either severe or mild/moderate PTS, they will remain in this state (23). In reality, it is likely that patients will pass from one state to another over the course of the disease.

The expected number of PH cases was estimated based on published incidence rates (18). Similar to PTS, expected cases of PH in any given year comprised PH related to incident cases of VTE occurring in that year plus PH related to incident cases of PE occurring in the previous two years. Rates of chronic PH expected to result in surgical intervention were applied to the estimate of incident cases of PE in order to estimate the total number of PH cases in a given year.

Estimation of the number of VTE-related deaths

Estimates of the number of VTE-related deaths included estimates of sudden death, death following diagnosed and treated disease, and death following undiagnosed, untreated disease. The number of deaths from recurrent cases was also estimated.

The number of VTE-related deaths was estimated from numbers of treated VTE events on the basis of an algorithm developed by Oster et al. (33). A simplified version of the algorithm is shown in Figure 2 (31, 33, 35). The key parameters defined by the algorithm are rates of diagnosed DVT, likelihood of progression from undiagnosed DVT (symptomatic and asymptomatic) to PE, and rates of death from diagnosed and undiagnosed VTE (symptomatic). For the purpose of the analysis, we assumed that diagnosed VTE was synonymous with treated VTE. We then applied the algorithm to the numbers of treated DVT and PE events in order to estimate the number of deaths related to diagnosed VTE in each of the six EU countries. This allowed us to estimate the number of expected deaths from cases of VTE that are not diagnosed as well as expected deaths from cases that are diagnosed. In order to assess whether the algorithm was applicable and reflected current understanding of VTE, it was reviewed by the advisory board. On the basis of this review, one parameter was adjusted. The likelihood of all DVT (initially asymptomatic and symptomatic) being detected and treated was adjusted from 16%, based on a report by Oster et al. (33), to 10% on the basis of more recent data (31, 35), which suggested that the original estimate overstates the current likelihood of clinical presentation and diagnosis.

Probabilistic sensitivity analyses

Probabilistic sensitivity analyses (PSAs) were conducted to assess the impact of uncertainty on the model results. One-way

Recurrent event/outcome	Year 1	Year 2	Year 3	Year 4	Year 5	Cumulative
Deep-vein thrombosis	0.104	0.030	0.017	0.017	0.017	0.185
Pulmonary embolism	0.025	0.007	0.004	0.004	0.004	0.044
Mild/moderate PTS	0.147	0.038	0.001	0.001	0.001	0.188
Severe PTS	0.026	0.017	0.017	0.017	0.017	0.094
Pulmonary hypertension	0.014	0.003	-	-	-	0.017

PTS, post-thrombotic syndrome.

Table 5: Probability of recurrence of venous thromboembolism (10, 34) and associated outcomes (10, 18) in the at-risk population.

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