Epidemiology of venous thromboembolic disease

Summary

Background The wide variations in reported incidence and mortality rates reflect gaps in the epidemiology of venous thromboembolic disease (VTD), a clinical entity with two different manifestations – deep vein thrombosis and pulmonary embolism. We reviewed recent studies and data sources to find the most useful estimates of its epidemiologic indicators in France.

Methods We used international medical databases to conduct a systematic literature review. Our search focused on the incidence and mortality rates of VTD in France and examined epidemiologic studies, autopsy studies, clinical trials, and national morbidity and mortality databases.

Results The annual incidence of deep vein thrombosis is approximately 120 per 100,000 in France and 60-100 per 100,000 worldwide; the annual incidence of pulmonary embolism, the principal serious complication of deep vein thrombosis, is between 60 to 111 per 100,000 in France and between 23 and 107 per 100,000 internationally. The reported mortality rate for VTD in France is 7.2 per 100,000, but estimates from international autopsy series suggest a pulmonary embolism prevalence among hospital patients of 0.8 to 1%.

Conclusion This study demonstrates the limitations of current epidemiologic knowledge about VTD. Improved information about this disease requires better case reporting and large population-based longitudinal cohort studies.

Despite progress in antithrombotic prophylaxis, venous thromboembolic disease (VTD) remains an important public health issue because of the morbidity and mortality associated with it. Epidemiologic data on VTD come primarily from autopsy or hospital-based studies, that is, surveys of populations at risk; there are far fewer population-based studies. Case identification most often requires diagnostic procedures available only in hospitals, and data specific to outpatient practice are rare. We conducted a systematic review of French and international studies for an inventory of the epidemiology of VTD. Our aim was to obtain useful estimates of the incidence and mortality associated with VTD in France.

Methods

The major international (Medline, Embase, Current Contents, Biosis, Cochrane) and French (Pascal and Francial) medical databases enabled us to search the literature. The search used the following key-words: venous thromboembolism, venous thromboembolic disease, pulmonary embolism, deep vein thrombosis, epidemiologic study, prevalence, incidence, and mortality. We considered all articles in English or French for the entire available period (1966-2003). Articles were selected if they met one of the following criteria: conducted in a French population, international population-based study of high methodological quality, autopsy study of a sufficiently large series, or meta-analysis of clinical trials of VTD prevention. This approach was completed by an analysis of various data sources not indexed in the international databases: recent international conferences and morbidity and mortality surveys by French public research agencies (PMSI, Inserm, INSEE-Credes).

Results

The search used predetermined selection criteria (based on inclusion of morbidity and mortality data for VTD) and identified 32 references to epidemiologic studies or clinical trials. We also located five references to data not indexed in the international medical databases.

DATA SOURCES

Epidemiologic studies

The French epidemiologic studies selected were all observational cross-sectional investigations of general populations, except for separate data for outpatients and at-risk populations (hospitalized patients). Four North American and two Swedish studies were also selected: all were longitudinal and all but two studies of hospitalized patients provided estimates from the general population.
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**Autopsy studies**

These retrospective studies, conducted between 1960 and 1990 in patients who died in the hospital, come mainly from English-speaking and Nordic countries. Several approaches were distinguished: studies aimed only at determining the number of cases of pulmonary embolism (PE) observed during autopsy without exploring causes of death \[^{17-19}\] and studies that distinguished fatal PE (direct cause of death) from those that contributed to the death \[^{20-25}\]. A single study \[^{26}\] separately identified incidental PE, unrelated to the death.

**Treatment trials**

Five large meta-analyses examined the principal clinical trials of antithrombotic prophylaxis published between 1992 and 2000. These studies assessed mortality attributable to VTD either directly, with a fatal PE rate \[^{27,28}\], or indirectly, by comparing overall mortality within the patient groups \[^{27-31}\].

**National morbidity and mortality databases**

French morbidity data for the general population come from the Credes survey \[^{32}\] (which measured household healthcare service consumption); the national medical informatics program (PMSI) compiles hospital data \[^{33}\]. INSERM publishes the French cause-of-death data, based on death certificates \[^{34}\].

**French epidemiologic data**

*Figure 1* presents the French data. Oger’s (EPI-GETBO) study \[^{8}\] was a prospective population-based study that applied exhaustive and objective criteria. It estimated the overall annual incidence of VTD at 180 per 100,000; that included an incidence of 120 per 100,000 for deep vein thrombosis (DVT) and of 60 per 100,000 for PE. The Credes survey \[^{32}\], conducted among the general population, calculated the annual incidence of DVT at 518 per 100,000; that of PE at 101 per 100,000. This estimate is very close to that from PMSI \[^{33}\] (between 96 per 100,000 and 111 per 100,000 from 1997 through 1999) for hospital populations. Dhote et al. \[^{7}\] studied patients hospitalized in internal medicine wards and calculated a DVT prevalence of 1.4% and a PE prevalence of 0.17%. In a similar setting, Bressolette et al. \[^{10}\] observed a prevalence of asymptomatic DVT at admission of 5.5%

**Principal international epidemiologic data**

According to the estimates accepted by the 1997 consensus conference on the prevention of venous thromboembolic accidents \[^{35}\], the annual incidence of DVT was 160 per 100,000, that of symptomatic (but not fatal) PE 20 per 100,000, and that of fatal PE (diagnosed post-mortem) 50 per 100,000. Anderson et al. \[^{12}\] report an annual incidence of 48 per 100,000 for DVT and 23 per 100,000 for PE. Given the proportion of VTD cases that are not hospitalized, they also consider that the annual incidence of DVT in the United States general population is probably around 245 per 100,000, an estimate fairly close to that of the Canadian study \[^{11}\], but higher than that of the Swedish \[^{15,16}\] and other American \[^{15,17}\] studies. The overall rate of PE in the large autopsy series ranges from 2.5% \[^{19}\] to 31.7% \[^{21}\], and the rate of fatal PE from 2.1 \[^{20}\] to 28.9% \[^{21}\]. Bergqvist et al. \[^{26}\] observed a rate of incidental (nonfatal) PE of 44.5%.

If we assume that the risk of thromboembolism for a hospitalized patient is independent of the risk of being hospitalized in case of death, we can rely on the results of autopsy studies to estimate the prevalence of PE among hospital patients. When we apply the global PE rate observed in the autopsy series to all of the patients hospitalized during the study period, the prevalence of PE among hospitalized patients ranges between 0.8% \[^{21}\] and 1% \[^{22}\]. *Figure 2* reports the mortality rate of PE observed in the principal meta-analysis.
lyses. Depending on the antithrombotic prophylaxis used, the overall mortality rate ranged between 0.52% and 6.5%, and the rate of fatal PE between 0% and 26%.

**Discussion**

The incidence of PE reported by the PMSI is quite similar to that in the Credes study. These French estimates are fairly close to the population-based rates for other countries. On the other hand, the PE rate from the prospective population-based Epi-Getbo study is less than half of these. Extrapolating these figures to the French population (59,096,259 persons in 1999), with an incidence rate between 60 and 100 per 100,000 and a lethality rate of 10% indicates that PE in France accounts for 35,000 to 66,000 new cases annually and causes 3,500 to 6,600 annual deaths. The upper range of this estimate appears closer to reality. The estimates of DVT incidence are much more scattered and vary by a factor of 10; figure 1 suggests that the Credes values are strongly overestimated and that the Epi-Getbo study results, which are close to those of international-population-based studies, should be accepted instead.

These two manifestations of VTD – deep vein thrombosis and pulmonary embolism – are not always considered separately; depending on the study, sometimes the first event diagnosed is the one that characterizes the VTD. The variation in the methods used to detect DVT and PE often prevents comparison between studies. While prevention practices improved consistently over time, they varied from one country to another. This review summarizes available epidemiologic data about VTD, which can best be described as a patchwork quilt of varying populations, study methods and results.

The data in the observational studies are most reliable when the population studied corresponds to a representative sample of the general population, when the diagnostic criteria employed are recognized and when diagnostic examinations are systematically performed. A selection bias is unavoidable in autopsy studies: the autopsies are not performed systematically and the population studied (hospital patients) is generally older or sicker than the general population.

Although randomization makes the estimates from the clinical trials more reliable, the population is still hospital-based and selected for thromboembolic risk factors or according to specific eligibility criteria. The morbidity and mortality databases have the advantage of yielding estimates that are not biased because they are based on systematic and exhaustive case reporting.

**Conclusion**

Improvement in epidemiologic knowledge of VTD worldwide requires more uniform and exhaustive case reporting. Only large longitudinal cohort studies in the general population can supply the reference rates of incidence and mortality that are essential to any epidemiologic approach to this condition.

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**What is already known**

- Venous thromboembolic disease in its two manifestations – deep vein thrombosis (DVT) and pulmonary embolism (PE) – is recognized as a relatively frequent disease. Because of the diagnostic difficulties and morbidity and mortality associated with it, prevention is essential.
- The epidemiologic data available in France come mainly from analysis of the circumstances of onset and genetic and acquired risk factors.
- There are fewer descriptive epidemiologic studies, and it is difficult to quantify the overall population currently affected by this multifactorial condition.

**What this article adds**

- French hospital statistics provide an estimate of the incidence of pulmonary embolism similar to that of the Credes study, and these French estimates are similar to the population-based rates of other countries, all with rates nearly twice as high as those from the Epi-Getbo study.
- Pulmonary embolisms in France probably account for 35,000 to 66,000 new cases each year and cause 3,500 to 6,600 deaths annually.
- The Credes figures for the incidence of deep vein thrombosis are highly overestimated; the results of the Epi-Getbo study in western France, similar to those in other countries, should be accepted instead.

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**Figure 2** Mortality rates based on the principal meta-analyses of the trials for thromboembolic risk prevention
References

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Epidemiology of venous thromboembolic disease