The Epidemiology of Venous Thromboembolism

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Abstract—Venous thromboembolism (VTE) occurs for the first time in approximately 100 persons per 100,000 each year in the United States, and rises exponentially from <5 cases per 100,000 persons <15 years old to ~500 cases (0.5%) per 100,000 persons at age 80 years. Approximately one third of patients with symptomatic VTE manifest pulmonary embolism (PE), whereas two thirds manifest deep vein thrombosis (DVT) alone. Despite anticoagulant therapy, VTE recurs frequently in the first few months after the initial event, with a recurrence rate of ~7% at 6 months. Death occurs in ~6% of DVT cases and 12% of PE cases within 1 month of diagnosis. The time of year may affect the occurrence of VTE, with a higher incidence in the winter than in the summer. One major risk factor for VTE is ethnicity, with a significantly higher incidence among Caucasians and African Americans than among Hispanic persons and Asian-Pacific Islanders. Overall, ~25% to 50% of patient with first-time VTE have an idiopathic condition, without a readily identifiable risk factor. Early mortality after VTE is strongly associated with presentation as PE, advanced age, cancer, and underlying cardiovascular disease. (Circulation. 2003;107:I-4–I-8.)

Key Words: venous thromboembolism • pulmonary embolism • epidemiology • prognosis • thrombosis • veins

Incidence of VTE

A number of studies have focused specifically on the epidemiology of VTE. Anderson et al determined the incidence of VTE in Worcester, Massachusetts, over an 18-month period in the mid 1980s by reviewing the hospital discharge records of all patients coded as having VTE, including both recurrent and first-time episodes. The number of cases (n=405) was small, and 97% were Caucasian.1 In Minnesota, Silverstein et al analyzed the medical records of all residents of Olmsted County who were diagnosed with VTE between 1966 and 1990 (n=2218). They categorized cases of VTE as definite, probable, or possible based on the level of objective confirmation. Importantly, a large number of cases of PE diagnosed at autopsy were categorized as definite VTE whether or not it was clinically symptomatic.2 Because the autopsy rate in Olmsted County is at least three times greater than the United States average, and because PE is reported in 7% to 30% of all autopsy series (median 15%),3 this type of VTE may have been overrepresented.

Kniffen et al used Medicare hospital discharge data from 1986 to 1989 to estimate the incidence of DVT and PE among individuals in the United States >65 years of age.4 The study included recurrent VTE and categorized cases as PE when this diagnosis was listed with a diagnosis of DVT. The Longitudinal Investigation of Thromboembolism Etiology study by Cushman et al combined 2 prospective cohort studies of individuals >45 years of age: the Cardiovascular Health Study and the Atherosclerotic Risk in Communities Study.5 Cases with confirmed VTE were identified, and all death records between enrollment (1987 to 1989) and 1997 were reviewed. Hansson et al followed a cross-sectional sample of men in Göteborg, Sweden, born in 1913, and analyzed the incidence of VTE based on hospital discharge diagnosis or autopsy records.6 In Malmö, Sweden, Nordström et al identified all patients with a venographic diagnosis of DVT during 1987 and reviewed the associated medical records to determine their demographic and clinical features. Cases of both initial and recurrent VTE were included.7 White et al have reported several studies using linked (1990 to present) hospital discharge records of California residents with a social security number (>95% of the population) who were hospitalized in any nonfederal hospital in California (~95% of the population) with DVT or PE.8–10 In these studies, race/ethnicity was defined based on coding by the hospital admissions office, but no laboratory or physiological data is included in this administrative data set. Although linked to a death registry, the cause of death among patients who died out of the hospital cannot be accurately determined.8

In these studies, involving predominantly Caucasian populations, the incidence of first-time symptomatic VTE directly standardized for age and sex to the United States population ranged from 71 to 117 cases per 100,000 population.1,2,11–14 The higher incidence, reported by Silverstein et al, likely reflects the large number of cases of PE detected at autopsy.2 As summarized below, the effects of race/ethnicity are so dominating that this incidence rate should not be extrapolated to non-Caucasians. Table 1 summarizes the major factors that affect the incidence of VTE.

Relative Incidence of DVT and PE

The most important methodological factor affecting the reported relative incidences of DVT and PE is reliance on
Summary of the Epidemiology of First-Time VTE

| Variable                              | Finding                                                                 |
|---------------------------------------|-------------------------------------------------------------------------|
| Incidence in Total Population (Assuming >95% Caucasian) | ~70–113 cases/100,000/year<sup>12,21–14</sup>                              |
| Age                                   | Exponential increase in VTE with age, particularly after age 40 years<sup>1,2,4,7</sup> |
| 25–35 years old                      | ~30 cases/100,000 persons                                               |
| 70–79 years old                      | ~300–500 cases/100,000 persons                                         |
| Gender                                | No convincing difference between men and women<sup>1,2</sup>             |
| Race/Ethnicity                        | 2.5–4-fold lower risk of VTE in Asian-Pacific Islanders and Hispanics<sup>9</sup> |
| Relative Incidence of PE vs DVT       | Absent autopsy diagnosis: ~33% PE; 66% DVT<sup>7,10</sup>                |
| Seasonal Variation                    | With autopsy: ~55% PE, 45% DVT<sup>7,16</sup>                          |
| Risk Factors                          | Possibly more common in winter and less common in summer<sup>24-26</sup>  |
| Recurrent VTE                         | ~25% to 50% “idiopathic” depending on exact definition<sup>1,5</sup>    |
| Death After Treated VTE              | ~15%–25% associated with cancer; ~20% following surgery (3 mo.)<sup>2,5,27</sup> |
|                                       | 6-month incidence: ~7%; higher rate in patients with cancer<sup>28-30</sup> |
|                                       | Recurrent PE more likely after PE than after DVT<sup>4,10,31</sup>       |
|                                       | 30 day incidence ~6% after incident DVT<sup>2,5,10</sup>                |
|                                       | 30 day incidence ~12% after PE<sup>1,32,33</sup>                       |
| Death strongly associated with cancer, age, and cardiovascular disease |

autopsy data. Most clinical studies that do not include autopsy data have reported the incidence of clinically diagnosed DVT to be approximately twice that of PE. Anderson et al reported an incidence of first-time DVT of 48 per 100,000, compared with 23 per 100,000 for PE (32% of VTE cases).<sup>1</sup> Murin et al found that 51,233 cases were admitted to California hospitals with VTE had DVT alone, whereas 21,625 (30%) had PE during the same period.<sup>10</sup> In a study of postoperative patients, 41% of VTE cases were PE.<sup>15</sup> In the Longitudinal Investigation of Thromboembolism Etiology study, 28% of VTE cases were PE.<sup>3</sup>

Studies that include a large number of VTE cases diagnosed by autopsy generally report a higher proportion of cases with PE than DVT. The yearly incidence of PE and DVT was 205 and 182 per 100,000, respectively, among men over age 50 as reported by Hansson et al.<sup>6</sup> and 69 and 48 per 100,000, respectively, as reported by Silverstein et al.<sup>2</sup> It is probable that autopsy data overestimate the incidence of PE by detecting asymptomatic cases, whereas reliance on clinical diagnosis probably underestimates the incidence.

**Effect of Race/Ethnicity**

Gore et al compared the prevalence of VTE at autopsy among 600 cases over age 40 years in Boston and an equal number in Kyushu, Japan. There was a strikingly higher prevalence of PE in North Americans (15%) than in Japanese (0.7%).<sup>15</sup>

In California, which has an ethnically diverse population including a large number of African Americans, Hispanics, and Asian-Pacific Islanders, White et al reported an annual incidence of idiopathic VTE in persons ≥18 years of age 23 per 100,000 among Caucasians; 29 per 100,000 among African Americans; 14 per 100,000 among Hispanics; and 6 per 100,000 among Asian-Pacific Islanders.<sup>9</sup> During 1996, the standardized incidence of first-time VTE was 86 per 100,000 among Caucasians; 93 per 100,000 among African-Americans; 37 per 100,000 among Latinos; and 19 per 100,000 among Asian-Pacific Islanders. These findings support the observations by Klatsky et al of a lower adjusted risk of VTE among Hispanics [risk ratio (RR) = 0.7, 95% confidence interval (CI) 0.3–1.5] and Asians (RR = 0.2, 95% CI 0.1–0.5) than in Caucasians in a large cohort followed prospectively in the Kaiser Health System in Northern California.<sup>16</sup>

The relatively low incidence of VTE in Asians and Hispanics has not been explained, but may relate to a lower prevalence of genetic factors predisposing to VTE, such as factor V Leiden in Asian populations (0.5%) compared with Caucasians (5%).<sup>17-19</sup> In venographic studies of patients recovering from hip replacement surgery, the incidence of asymptomatic VTE in Asians appears comparable with that in North America,<sup>20-22</sup> suggesting that the difference in VTE incidence may be related to less efficient inactivation of coagulation by activated protein C or less fibrinolytic activity among Caucasians. The lower incidence of VTE in Hispanics than in African Americans cannot be explained by a lower prevalence of factor V Leiden, as this genetic condition is present in ~2% of Hispanic and <1% of African Americans.<sup>17,23</sup>

**Effect of Age**

A number of published studies have shown that the incidence of first-time VTE rises exponentially with age, from a negligible rate (<5 per 100,000 per year) among children <15 years of age to values in the range of 450 to 600 per 100,000 per year (~0.5%/year) among individuals over the age of 80 years.<sup>1,2</sup> As shown in Figure 1, the incidence increases dramatically after age 60.<sup>1</sup>

Among individuals 50 to 59 years old, Anderson et al observed an incidence of first-time plus recurrent VTE of 62 per 100,000, whereas for patients in this same age range, Silverstein et al observed a much higher incidence of 122 per 100,000 among women and 147 per 100,000 among men. In the study reported by Hansson et al, the observed incidence was 132 per 100,000 population age 50–59.<sup>6</sup> Among indi-
and women.7 Using the California Discharge Data set we observed no such seasonal variation in the incidence of DVT.11 Using a large French discharge data set (n = 100,000); the difference was due largely to a higher incidence (78 per 100,000 adults over age 18) than in men (63 per 100,000 per year).2 Nordström et al reported that the incidence of DVT alone was 765 cases per 100,000 population during a single year (unknown proportion with recurrent DVT);7 and Kniffin et al reported an annual incidence of 442 cases per 100,000 population (includes individuals with recurrent VTE).4 Overall, Nordström et al estimated that the cumulative probability of developing VTE between ages 50 and 80 was 10.7% for Swedish men.

Effect of Sex
Although use of oral contraceptives and postmenopausal hormone replacement have been associated with VTE in women, published data suggest no consistent differences in the incidence of VTE among men and women.

Anderson et al found a similar incidence in both sexes (Figure 1).1 Silverstein et al noted a slightly higher incidence rate among younger women,2 and a modest predilection among older men. Cushman et al reported similar incidences among men and women except for a 2-fold higher rate in men over age 75.5 Among patients >65 years, Kniffin et al reported that women had a slightly higher relative risk of DVT (RR = 1.05, 95% CI 1.0–1.1) and a lower risk of PE (RR = 0.86, 95% CI 0.82–0.90).4 Nordström et al reported no significant difference in the incidence of DVT between men and women.7 Using the California Discharge Data set we noted a slightly higher incidence of first-time VTE in women (78 per 100,000 adults over age 18) than in men (63 per 100,000); the difference was due largely to a higher incidence in women >80 years old. In the absence of a consistent difference among studies, therefore, the incidence of VTE is probably approximately equal in men and women.

Seasonal Variation
Although some reports have described a higher incidence of fatal PE during the winter months,24,25 Bounameaux et al observed no such seasonal variation in the incidence of DVT.11 Using a large French discharge data set (n = 127,318), Boulay et al found 10% to 15% more admissions during winter months and 10% to 15% fewer admission during the summer.26 Additional studies are needed to confirm this finding. Assuming the amount of physical activity in a population decreases in the winter, it is possible that this finding demonstrates an inverse relationship between physical activity and development of VTE.

Incidence of Idiopathic Versus Secondary VTE
Although Anderson et al did not classify VTE cases as idiopathic or secondary, they did note that 15% of the patients in their study had cancer. In the study by Cushman et al, 47% of 304 cases had idiopathic VTE, defined as no associated cancer, antecedent trauma, or recent surgery or immobilization.5 Twenty-five percent of their cases had undergone antecedent surgery, and 25% had cancer. In a recent analysis of the data from Silverstein et al, Heit et al reported that only 26% of cases were idiopathic, and attributed 59% to immobilization or nursing home residence, 18% to cancer, 12% to trauma, and the remainder to medical illness, stroke, or central venous lines or pacemakers.27 In our analysis of patients in California hospitalized with first-time VTE, 18% had malignancy, 23% had undergone surgery within 2 months, 15% developed VTE during a hospitalization for medical illness, 2% had major trauma, and a 41% were idiopathic. Thus, the proportion of patients with VTE categorized as idiopathic falls in the range of 26% to 47% of first-time cases; the exact figure depends partly on the definitions of idiopathic and secondary VTE.

Recurrent VTE
Cushman et al found the first-year incidence of recurrent VTE was 7.7% overall and 7.8% among patients with idiopathic VTE; patients with cancer had a higher rate of recurrence (14.0% per year).5 In a prospective cohort study of 355 patients with DVT, Prandoni et al reported recurrent VTE in 8.6% after 6 months and 30.3% after 8 years.28 Hansson et al reported rates of recurrent VTE of 7.0% at 1 year and 22.0% at 5 years.29 In the Olmsted county study, Heit et al found the incidence of recurrent VTE was 10.1% at 6 months, 12.9% after 1 year, and 30.4% after 10 years.30 This relatively high recurrence rate may reflect changes in methods of diagnosis and treatment of VTE over the 25-year period during which the data were collected.

Using the California Patients Discharge Data Set, the 6-month recurrence rate of VTE was 6.4% in the cohort of patients hospitalized for DVT (n = 51,233) and 5.8% in the cohort initially hospitalized for PE (n = 21,625).10 When deaths were censored according to the Kaplan–Meier technique, VTE recurrence rates were identical in the 2 cohorts. Figure 2 shows that recurrent VTE is most likely in the weeks after initial hospitalization for DVT. Heit et al also reported a higher incidence of recurrent VTE in the period immediately after diagnosis with a gradual reduction in the recurrence rate over time.30

In the study by Murin et al,10 86% of recurrent events after DVT were DVT, whereas 66% of recurrent events after PE were PE. Kniffin et al reported similar relationships, which have also been observed in randomized clinical studies.31
Finally, in the study by Hansson et al of 591 patients with DVT, 77% of recurrent events were DVT.29

Mortality after Initial VTE
Case fatality rates are difficult to interpret using data collected retrospectively, particularly when autopsy data are used to identify patients with PE. Prospective data also may be difficult to interpret when autopsies are not performed on patients who die of unexplained causes. Cushman et al noted a 28-day case-fatality rate of 9.4% after first-time DVT and 15.1% after first-time PE.3 Among patients with idiopathic VTE, the 28-day rate was 5.2% compared with 7.3% after secondary VTE and 25.4% among patients with cancer. In our study, the 6-month fatality rate was 10.5% among patients with DVT and 14.7% among those with PE.30 The cohort of Silverstein et al had 30-day case-fatality rates of 5.5% for patients with DVT and 8.0% for those with PE not diagnosed at autopsy.2 The case-fatality rate of recurrent VTE may differ from that of initial VTE.31 In the study by Prandoni et al, of 355 patients with first-time DVT, 16.7% of patients had died at 1 year, with cancer the most frequent cause.28 Siddique et al recently analyzed the 30-day case-fatality rate after primary diagnosis of PE among individuals >65 years of age and reported a rate of 16.1% in African Americans and 12.9% in Caucasians.32 Patients diagnosed with PE during hospitalization for another condition had a higher case-fatality rate (32.5%) than those admitted for PE. In the study by Anderson et al, 11.6% of patients died during the index hospitalization, 5% of those with DVT and 23% of those with PE.1 During long-term (2 to 3.5 years) follow-up, however, the mortality rate was 25% for patients with PE and 32% for patients with DVT. Mortality was strongly associated with age, and PE was listed on the death certificate as contributory in only 4 of the 108 deaths. Finally, the International Cooperative Pulmonary Embolism Registry was established to determine mortality rates of PE and to identify baseline factors associated with death. The 3-month overall crude mortality rate was 17.4%; 45.1% of deaths were ascribed to PE.33 After excluding patients in whom PE was first discovered at autopsy, the 3-month overall mortality rate was 15.3%. Systolic arterial hypotension, congestive heart failure, cancer, tachypnea, right-ventricular hypokinesis on echocardiography, chronic obstructive pulmonary disease, and age >70 years were significantly associated with increased mortality risk in patients with PE.

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