Deep Vein Thrombosis and Pulmonary Embolism in Two Cohorts: The Longitudinal Investigation of Thromboembolism Etiology

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PURPOSE: To determine the incidence of deep vein thrombosis and pulmonary embolism in two cohorts representing regions of the United States.

METHODS: The sample comprised 21,680 participants of the Atherosclerosis Risk in Communities study and the Cardiovascular Health Study. Subjects were aged ≥45 years, resided in six communities, and were followed for 7.6 years. All hospitalizations were identified and thromboses were validated by chart review.

RESULTS: The age-standardized incidence of first-time venous thromboembolism was 1.92 per 1000 person-years. Rates were higher in men than women, and increased with age in both sexes. There was no antecedent trauma, surgery, immobilization, or diagnosis of cancer for 48% (175/366) of events. The 28-day case-fatality rate was 11% (29/265) after a first venous thromboembolism and 25% (17/67) for cancer-associated thrombosis. The recurrence rate 2 years after a first venous thromboembolism was 7.7% per year (95% confidence interval [CI]: 4.5% to 10.9% per year). Cancer was the only factor independently associated with 28-day fatality (relative risk [RR] = 5.2; 95% CI: 1.4 to 19.9) or recurrent thrombosis (RR = 9.2; 95% CI: 2.0 to 41.7).

CONCLUSION: The incidence of venous thromboembolism in this cohort of middle- and older-aged subjects was similar to that observed in more geographically homogenous samples. Half of cases were idiopathic. Short-term mortality and 2-year recurrence rates were appreciable, especially among subjects with cancer. Based on this study we estimate that 187,000 cases of first-time venous thromboembolism are diagnosed yearly in the United States among those aged 45 years or older. **Am J Med. 2004;117:19–25.** ©2004 by Elsevier Inc.

Venous thromboembolism is the third most common life-threatening cardiovascular disease in the United States (1). Although several studies have reported incidence rates for thromboembolism (2–9), most had narrow geographical representation or used administrative data to identify cases. There is little information describing precipitants and conditions present at diagnosis of thrombosis. Few studies addressed differences in demographic characteristics comparing idiopathic and secondary thrombosis. Further, mortality and recurrence rates were mainly described in geographically defined samples (2,10–12), single institutions (3,13–15), or clinical trials.

The Longitudinal Investigation of Thromboembolism Etiology (LITE) evaluated the occurrence of and risk factors for thrombosis in two population-derived cohorts. In a previous report we presented incidence rates excluding participants with a history of cancer or who were taking anticoagulants (16). Here, incidence rates and associated features of first-time and recurrent thrombosis are presented for the entire cohort.

METHODS

Subjects

The study combined population-based cohorts from two studies: the Cardiovascular Health Study (CHS) and Atherosclerosis Risk in Communities (ARIC) study. Participants from six communities were followed: Forsyth County, North Carolina; Washington County, Maryland; suburban Minneapolis, Minnesota; Jackson, Mississippi; Sacramento County, California; and Pittsburgh, Pennsylvania (17,18). Between 1987 and 1989, ARIC enrolled 15,792 subjects aged 45 to 64 years (4266 African Americans). In 1989–1990 and 1992–1993, CHS enrolled 5888 subjects aged ≥65 years (924 African Americans). Thrombosis events were identified through December

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Table 1. Validation Rates of Discharge Codes Used to Identify Cases of Venous Thromboembolism

Discharge Diagnosis (ICD-9-CM Code)	No. of Validated Events/ No. of Reviewed Charts (% Validated)
Pulmonary embolism and infarction (415.1x)	110/153 (72)
Phlebitis, thrombophlebitis (451)	
Deep vessels of lower extremities (451.1x)	60/81 (74)
Lower extremities, unspecified (451.2)	6/30 (20)
Other sites (451.8x)	2/15 (13)
Unspecified site (451.9)	1/9 (11)
Other venous embolism and thrombosis (453)	
Budd-Chiari syndrome (453.0)	1/1 (100)
Thrombophlebitis migrans (453.1)	1/2 (50)
Vena cava (453.2)	3/6 (50)
Other specified veins (453.8)	155/195 (80)
Unspecified site (453.9)	2/7 (29)
Other complication of internal prosthetic device, implant, or graft (996.7x)	11/206 (5)
Peripheral vascular complications (997.2)	1/30 (3)
Other vascular complications of medical care (999.2)	0/3 (0)
Placement of vena cava filter (38.7)	4/7 (57)
Total	357/756 (47)

ICD-9-CM = *International Classification of Diseases, Ninth Revision, Clinical Modification.*

31, 1996, in ARIC, and through June 30, 1997, in CHS. Informed consent was obtained from participants, with approval of methods from the institutional review committees at each study center.

Case Ascertainment

The ARIC cohort was followed by clinic visits every 3 years, annual telephone calls, and surveillance of community hospitals. Hospitalizations were identified by participant report and systematic search of local hospital discharges for cohort members. In CHS, follow-up involved alternating clinic visits and telephone calls every 6 months. Hospitalizations were also identified using Medicare records. For all hospitalizations, *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) discharge codes were recorded and used to identify possible cases of thrombosis (Table 1).

Early during review of records, cases identified only by vascular complications codes (996.7x, 997.2, 999.2) usually had peripheral artery disease. Thus, record abstractors were given the option of not forwarding such records if there was no diagnostic test for thrombosis or thrombosis was not recorded as a discharge diagnosis. We attempted to ascertain missed cases by reviewing hospital records for self-report of thrombosis during follow-up, and by reviewing hospital and autopsy records for deaths reportedly related to thrombosis.

Information from hospital records, and records from hospitalizations within 3 months of a potential admission for thrombosis, were reviewed independently by two physicians (MC, ARF); differences in classification were resolved by discussion. Clinical diagnoses without objective tests were not validated as cases. Definite deep vein thrombosis was defined as a positive duplex ultrasound or venogram or, in rare cases, by computed tomography. Probable deep vein thrombosis required a positive Doppler ultrasound or impedance plethysmography. Upper extremity thrombosis included thrombosis of arm veins; superior vena cava; or internal jugular, subclavian, innominate, or axillary veins. Pulmonary embolism was classified using results of ventilation/perfusion scans (19), angiography, or, rarely, computed tomography or autopsy. Indeterminate scans without angiograms, and positive perfusion scans without ventilation scans, were not considered cases.

For confirmed cases, we recorded physician statements on past history of thrombosis; cancer diagnosed within 1 year before or after thrombosis; previous cancer; and stated history of myocardial infarction, heart failure, renal failure, major trauma, major surgery, marked immobility (coma, paralysis, orthopedic-induced limitation, bedrest), autoimmune disease, hospital admission, or chemotherapy all within 90 days before thrombosis.

Thrombosis events were classified as idiopathic or secondary (occurring within 90 days of major trauma, surgery, or marked immobility, or associated with active cancer or chemotherapy), and first or recurrent. Recurrent events were those with prior thrombosis stated in the medical record, or those with prior validated thrombosis.

For most analyses, concurrent deep vein thrombosis and pulmonary embolism was classified as pulmonary embolism.

Reliability of thrombosis classification was assessed by re-review of 37 abstracted charts, 17 with equivocal or positive diagnostic tests. There were four disagreements, two regarding classification as probable or definite deep vein thrombosis, and two regarding classification as idiopathic or secondary.

Statistical Analysis

Incidence rates were calculated for first diagnosis of venous thromboembolism, then were age-standardized to the 2000 U.S. population aged ≥45 years (www.census.org). Chi-squared tests or analysis of variance were used to analyze categorical data. Incidence rates of recurrence or death after first thrombosis were computed for three groups: idiopathic, cancer-associated, and noncancer-associated secondary thrombosis. Mortality during 28 days after admission for thromboembolism or recurrent thrombosis was analyzed according to participant characteristics using Cox proportional hazards modeling. In the latter models, participants who died or were lost to follow-up were censored.

RESULTS

Validation of Cases

Of 938 discharge records identified, 366 cases were validated in 304 subjects, with similar validation rates by cohort. There were 267 cases of deep vein thrombosis, 58 cases of pulmonary embolus, and 41 cases of both conditions. Of the 308 cases of deep vein thrombosis, 44 were probable and 264 were definite; these were considered together for all analyses. The ICD-9-CM codes with the highest proportions of validated thromboses were 415.1, 451.1, and 453.8 (Table 1).

Twenty death certificates listed pulmonary embolus for patients with no hospitalization for thrombosis. For the 4 CHS decedents, all available discharge summaries were reviewed, yielding 1 case of validated thrombosis. For the 16 ARIC decedents, 2 had autopsy reports documenting pulmonary embolus, but they were excluded because clinical information was unavailable. Nineteen participants reported venous thrombosis and warfarin use without hospitalization for a potential thrombosis. Review of all discharge summaries of the 15 CHS subjects revealed 4 cases of validated thrombosis. Review of discharge summaries from 40 of 214 participants who reported thrombosis but not warfarin use yielded no cases.

Incidence of Venous Thromboembolism

There were 304 subjects who had at least one venous thromboembolism during 7.6 years of follow-up: 265 with a first lifetime episode and 39 with a recurrent episode. Exclusion of those with a recurrent episode and those who reported thromboembolism at baseline yielded 164,718 person-years of observation. The unadjusted incidence rates were 1.61 per 1000 person-years (95% confidence interval [CI]: 1.43 to 1.81 per 1000 person-years) for first lifetime venous thromboembolism, 1.17 per 1000 person-years for deep vein thrombosis alone, and 0.45 per 1000 person-years for pulmonary embolism with or without deep vein thrombosis. Rates were 1.20 per 1000 person-years in ARIC and 3 per 1000 person-years in CHS. Based on the population age distribution, these incidence rates would translate into 187,000 episodes of first venous thromboembolism per year among persons ≥45 years old in the United States, with an age-adjusted incidence of 1.92 per 1000 person-years.

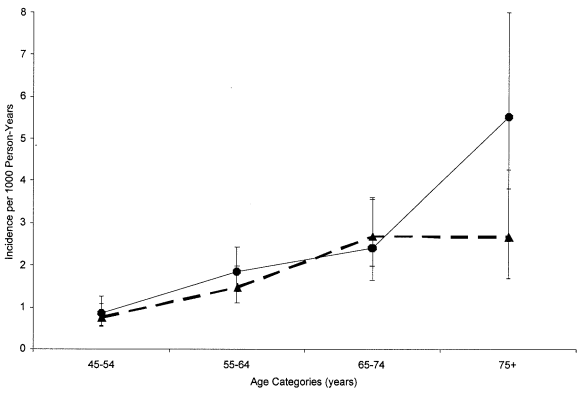

Figure. Sex- and age-specific incidence rates of validated venous thromboembolism in the Longitudinal Investigation of Thromboembolism Etiology. The black line and circles represent men; the dashed line and triangles represent women. Error bars represent 95% confidence intervals.

The incidence of first lifetime thromboembolism increased with age, with rates among subjects ≥65 years old more than three times those in subjects aged 45 to 54 years (Figure). Rates were similar in men and women, although above age 75 years the rate in men was twice that in women (5.5 [95% CI: 3.8 to 8.0] per 1000 person-years vs. 2.7 [95% CI: 1.7 to 4.3] per 1000 person-years).

Classification of Venous Thromboembolism, Associated Conditions, and Case Fatality

Among all 366 validated thromboses, 175 (48%) were idiopathic and 191 (52%) were secondary (Table 2). Most deep vein thromboses were in the lower extremities and were equally likely to be in either lower extremity ($P = 0.45$).

Most of the 191 cases of secondary venous thromboses were associated with more than one underlying condition (Table 3). These included cancer (48%, n = 91), hospitalization (52%, n = 99), surgery (42%, n = 80), and major trauma (6%, n = 11). Most conditions occurred with similar frequency in patients with deep vein thrombosis or pulmonary embolism, except for chemotherapy,

Table 2. Characteristics of Validated Venous Thromboembolism Cases*

Characteristic	Deep Vein Thrombosis (n = 267)	Pulmonary Embolism† (n = 99)
	Number (%)	
Lower extremity	243 (91)	—
Right/left/both	103 (42)/114 (47)/26 (11)	
Proximal/isolated distal/unknown	224 (92)/18 (7)/1 (<1)	
Upper extremity	18 (7)	—
Other site	6 (2)	—
Idiopathic/secondary	125 (47)/142 (53)	50 (51)/49 (49)
Incident/recurrent	217 (81)/50 (19)	87 (88)/12 (12)

* For deep vein thrombosis, 267 events occurred among 217 subjects. For pulmonary embolism, 99 events occurred among 87 subjects.
† Includes 41 pulmonary embolism cases also diagnosed with deep vein thrombosis, and not included under "Deep Vein Thrombosis" in the Table.

which was twice as common among those who had been diagnosed with deep vein thrombosis.

Among incident cases, 116 were idiopathic and 149 secondary. Participants with incident idiopathic or secondary thrombosis were older at baseline than were those who remained thrombosis free (Table 4). Otherwise, these groups were similar, except for self-reported pre-baseline cancer, which was more common in those with secondary thrombosis than in those without thrombosis.

The 28-day case-fatality rate among all 366 cases of thrombosis was 10% (95% CI: 7% to 13%; n = 38). Rates ranged from 5% to 25% according to thrombosis type among the 265 subjects with first lifetime thrombosis (Table 5). Cancer was the only factor independently associated with increased mortality (Table 6).

Table 3. Associated Conditions in Secondary Venous Thromboembolism*

Condition	Deep Vein Thrombosis (n = 142)	Pulmonary Embolism (n = 49)	*P* Value†
	Number (%)		
Major surgery	56 (39)	24 (49)	0.19
Major trauma	4 (3)	7 (14)	0.03
Cancer	72 (51)	19 (39)	0.28
If yes, on chemotherapy	23 (32)	3 (16)	0.001
Hospitalization	73 (51)	26 (53)	0.46
Marked immobility	24 (17)	6 (12)	0.27
Myocardial infarction	4 (3)	4 (8)	0.11
Heart failure	11 (8)	5 (10)	0.50
Autoimmune disease	9 (6)	1 (2)	0.28
Renal failure	11 (8)	1 (2)	0.30
Stroke	11 (8)	1 (2)	0.27
Other‡	33 (23)	11 (22)	0.47
Number of conditions			
1	50 (35)	17 (35)	
2	58 (41)	20 (41)	
3	24 (17)	9 (18)	
4	8 (6)	3 (6)	
5	2 (1)	0	

* All conditions within 90 days of thrombosis, except cancer, which was within 1 year before or after thrombosis.
† *P* values comparing deep vein thrombosis with pulmonary embolism, adjusting for age.
‡ Including catheter or pacemaker (n = 8); vein obstruction due to mass, fibrosis, or hematoma (n = 6); having a cast (n = 2); tamoxifen for cancer (n = 5); possible cancer (n = 4); and other medical problems (n = 19).

Recurrent Events

There was an average of 2.2 years of subsequent observation until recurrent thrombosis or the end of follow-up for the 265 subjects with first lifetime thromboembolism. Forty-five of these subjects had recurrent thrombosis, a

Table 4. Baseline Characteristics of Participants with First Venous Thromboembolism and Those Remaining Thrombosis Free during Follow-up*

Characteristic	Idiopathic Thrombosis (n = 116)	Secondary Thrombosis (n = 149)	Thrombosis Free (n = 21,376)
	Number (%) or Mean ± SD		
Age (years)	63.0 ± 10.4†	63.6 ± 10.3†	59.2 ± 10.1
Male sex	54 (46)	71 (48)	9246 (44)
From ARIC	85 (73)	109 (73)	15,618 (73)
Nonwhite race	30 (26)	40 (27)	5199 (24)
Self-reported history of cancer	12 (10)	20 (13)‡	1672 (8)
Prevalent coronary heart disease	12 (10)	13 (9)	1772 (8)

* Sex, race, self-reported history of cancer, and prevalent coronary heart disease estimates areadjusted for age.
† $P = 0.0001$ vs. thrombosis-free group.
‡ $P \leq 0.01$ vs. thrombosis-free group.
ARIC = Atherosclerosis Risk in Communities.

Table 5. Case Fatality at 28 Days after a First Lifetime Venous Thromboembolism

Type of Thrombosis	No. of Deaths/ No. of Events	Case Fatality (%) (95% Confidence Interval)
Deep vein thrombosis or pulmonary embolism	29/265	11 (7–15)
Deep vein thrombosis	18/192	9 (5–14)
Pulmonary embolism	11/73	15 (7–23)
Idiopathic deep vein thrombosis or pulmonary embolism	6/116	5 (1–9)
Secondary, noncancer-related deep vein thrombosis or pulmonary embolism	6/82	7 (2–13)
Secondary, cancer-related deep vein thrombosis or pulmonary embolism	17/67	25 (15–36)

rate of 7.7% per year (95% CI: 4.5% to 10.9%). Rates were slightly higher in men than women (8.1% per year [95% CI: 3.4% to 12.8%] vs. 7.3% per year [95% CI: 3.0% to 11.7%]), as well as in those older than 65 years than in those who were younger at baseline (9.3% per year [95% CI: 4.0% to 14.6%] vs. 6.5% per year [95% CI: 2.6% to 10.5%]). Of the 116 idiopathic events, there were 21 recurrences, a rate of 7.8% per year (95% CI: 2.9% to 12.7%). Among 67 cancer-associated events, there were 12 recurrences, a rate of 14.2% per year (95% CI: 5.9% to 22.6%). Among 82 cases of noncancer-associated secondary thrombosis, there were 12 recurrences, a rate of 5.2% per year (95% CI: 0.4% to 10.0%). Considering all these factors, cancer was the only statistically significant predictor of recurrence (Table 6).

DISCUSSION

We merged two population-based studies and validated cases of venous thrombosis in adults aged 45 years or older, and found that the age-adjusted incidence of first lifetime thrombosis was 1.92 per 1000 person-years, which translates into nearly 190,000 first thromboses each year in persons 45 years or older in the United States.

Table 6. Risk Factors for Death during 28 Days, and for Recurrence during 2.2 Years, after a First Venous Thromboembolism (n = 265)

Characteristic	28-Day Fatality	Recurrent Thrombosis
	Hazard Ratio (95% Confidence Interval)	
Age ≥65 years	1.0 (0.2–4.1)	1.6 (0.4–6.8)
Male sex	2.3 (0.6–9.4)	1.8 (0.5–7.2)
Thrombosis type (deep vein thrombosis vs. pulmonary embolism)	0.9 (0.2–3.6)	2.2 (0.5–9.4)
Presence of cancer	5.2 (1.4–19.9)	9.2 (2.0–41.7)

Thrombosis rates increased with age, and were more than twofold higher in those older than 65 years. The 28-day fatality after a first thrombosis was 11%, with cancer conferring an increased mortality risk. The 2.2-year recurrence rate after a first thrombosis was substantial at 7.7% per year.

Our observed incidence of thromboembolism compares with rates for adults in Worcester, Massachusetts (0.7 per 1000 person-years) (3); Malmö, Sweden (1.6 per 1000 person-years) (4); Olmsted County, Minnesota (1.2 per 1000 person-years) (9); Göteborg, Sweden (1.8 per 1000 person-years) (6); and Brest, France (1.8 per 1000 person-years) (20). A recent overview reported a rate of 5 per 10,000 for first deep vein thrombosis (without pulmonary embolus) for the entire age spectrum (21). If the LITE incidence rate was extrapolated to the entire age spectrum, assuming an exponential increase with age, the rate for deep vein thrombosis and pulmonary embolism would be 7.1 per 10,000.

Secondary thrombosis was more common than the idiopathic form of the disease in LITE. However, characteristics of patients with idiopathic and secondary thrombosis were similar. The majority of cases of secondary thrombosis had more than one underlying condition, with surgery and cancer the most common. These findings suggest that improved thromboprophylaxis in these settings in all demographic groups might substantially lower the incidence of thrombosis (9,22). Based on the contribution of cancer to secondary thrombosis, further information on optimal prophylaxis methods among cancer patients is needed.

The 2-year recurrence rates of thrombosis observed here were similar to those reported with similar follow-up in one study (14) but higher than in others (5,6,11,13). Differences among studies could represent secular trends, because our study was performed later. Compared with most studies, a larger proportion of cases of thrombosis in our study was associated with cancer. In one study (11), recurrence rates were similar to ours when "possible recurrences" were included. In two stud-

ies (6,13), recurrence rates were based on less than 20 recurrences. We found that cancer was the only factor associated with the risk of recurrence. Although our study lacked statistical power, the lower recurrence rate for secondary noncancer-associated thrombosis than for idiopathic thrombosis is consistent with other reports (14). The risk of recurrence associated with cancer here was higher than in a recent inception cohort of thrombosis patients with 1 year of follow-up (23). Despite insufficient power, our findings are consistent with others reporting higher recurrence rates with age (11,13) and among men (11).

The 28-day case-fatality rate in LITE was substantial (10%) and was generally similar to rates in other studies, although direct comparisons are difficult due to differing lengths of follow-up defining case fatality (3,5,6,10,14,15,24,25). Studies that included autopsy-defined pulmonary embolism (6,10,25) reported rates of about 50%, which were similar to ours when autopsy cases were excluded. We confirmed that cancer patients have high case-fatality rates for thrombosis (10,14,25), but could not confirm an association of older age with case fatality (3,10,13,25), perhaps because all participants were aged ≥45 years at enrollment.

We underestimated the incidence rate of thrombosis for several reasons. First, as in most studies, patients with fatal or nondiagnosed events were underascertained. Second, cases of thrombosis treated outside the hospital were not ascertained; however, outpatient treatment was rarely used during our study. Third, we applied stringent case validation criteria, especially for pulmonary embolism, and several reviewed cases had typical clinical findings but nondiagnostic radiology. It is likely that many of these were thrombosis cases. Fourth, persons in long-term care facilities were not enrolled; the incidence of thrombosis in these settings is probably above average.

Several limitations of our study merit consideration. Assessment of associated conditions and classification as idiopathic or secondary thrombosis were limited by contents of the medical record. Classification of thrombosis was limited based on the radiologic evaluations typically used in the United States. We could not classify cases into groups of isolated deep vein thrombosis, isolated pulmonary embolism, or pulmonary embolism combined with deep vein thrombosis, a classification that appears to have implications for risk-factor associations (26). Assessment of recurrent thrombosis was limited by nonstandardized follow-up procedures in this general practice setting. We did not have information to study quality or duration of anticoagulation. During the study period, 3 to 6 months of oral anticoagulation was typically used for secondary prophylaxis of thrombosis. Larger studies, similar to those of Prandoni and Goldhaber et al (14,25), which are designed to address these limitations, would be useful.

Strengths of this study include a population-based, prospective assessment involving a wide geographic distribution in the United States. Case validation was systematic. Although nonwhites (mainly African Americans) were well-represented, only 70 cases of thrombosis were identified in this group, so further study is required (5,8,16).

Our results underscore the impact of venous thrombosis on public health in the United States, including the associated substantial short-term mortality. Areas requiring further study include the optimal management and prevention of thrombosis among patients at high risk of first and recurrent events, especially cancer patients, who comprised one third of those with incident thrombosis in this study.

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