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Secular trends in occurrence of acute venous thromboembolism: the Worcester venous thromboembolism study (1985 to 2009)

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Abstract

BACKGROUND—The clinical epidemiology of venous thromboembolism has changed recently due to advances in identification, prophylaxis, and treatment. We sought to describe secular trends in occurrence of venous thromboembolism among residents of the Worcester, Massachusetts, metropolitan statistical area (WMSA).

METHODS—Population-based methods were used to monitor trends in event rates of first-time or recurrent venous thromboembolism in 5025 WMSA residents diagnosed with acute pulmonary embolism and/or lower-extremity deep vein thrombosis during 9 annual periods between 1985 and 2009. Medical records were reviewed by abstractors and validated by clinicians.

RESULTS—Age- and sex-adjusted annual event rates for first-time venous thromboembolism increased from 73 (95% CI 64–82) per 100,000 in 1985/1986 to 133 (122–143) in 2009, due mostly to an increase in pulmonary embolism. The rate of recurrent venous thromboembolism decreased from 39 (32–45) in 1985/1986 to 19 (15–23) in 2003, and then increased to 35 (29–40) in 2009. There was an increasing trend in using non-invasive diagnostic testing, with about half of tests being invasive in 1985/1986 and almost all non-invasive by 2009.

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CONCLUSIONS—Despite advances in identification, prophylaxis, and treatment between 1985 and 2009, the annual event rate of venous thromboembolism has increased and remains high. While these increases may be partially due to increased sensitivity of diagnostic methods, especially for pulmonary embolism, it may also imply that current prevention and treatment strategies are less than optimal.

Keywords

venous thromboembolism; venous thrombosis; pulmonary embolism; incidence; outcomes research

Venous thromboembolism, comprising deep vein thrombosis and pulmonary embolism, is associated with increased long-term morbidity, functional disability, and all-cause mortality.¹ Over three decades ago, venous thromboembolism was estimated to be the third most common acute cardiovascular event after the acute coronary syndromes and ischemic stroke.² Recent data on the clinical epidemiology of venous thromboembolism are, however, limited.³

Considerable variation exists in estimates of the annual incidence rates of venous thromboembolism, derived from population-based studies and hospital discharge or health-insurance claims databases.³ Major advances have occurred in identifying patients at increased risk for venous thromboembolism, in thromboprophylaxis, and in diagnostic methods and treatments.^{3–9} Growing awareness of venous thromboembolism as an important public-health problem became the impetus for evidence-based guidelines for appropriate prevention and treatment, which have been revised over time.^{10–11} These advances have likely influenced the reported frequency of venous thromboembolism.

Using data from the Worcester venous thromboembolism study (1985 to 2009), we describe 25-year trends in event rates, patient characteristics, and use of different diagnostic approaches among residents of the Worcester, Massachusetts, metropolitan statistical area (WMSA) diagnosed with clinically recognized acute venous thromboembolism.

METHODS

The Worcester venous thromboembolism study employed population-based surveillance methods to monitor trends in event rates of first-time or recurrent episodes of pulmonary embolism and/or deep vein thrombosis, including management strategies, case-fatality rates, and recurrences after the index event among WMSA residents.^{12–15} Reflecting the evolution of the standard care of acute venous thromboembolism, Cohort-I included all hospital inpatients discharged with a primary/secondary diagnosis of venous thromboembolism during two 18-month periods, July 1985 to December 1986, and July 1988 to December 1989. Cohort-II included hospitalized patients and outpatients diagnosed with venous thromboembolism based on outpatient, emergency department, radiology department, or diagnostic laboratory encounter during 1999, 2001, 2003, 2005, 2007, and 2009. Medical records were reviewed by trained abstractors and validated by clinicians.

This study was approved by the institutional review committee at participating hospitals.

Venous thromboembolism Definition

Both cohorts used International Classification of Disease, 9th revision, codes to identify eligible acute cases of pulmonary embolism and/or deep vein thrombosis (Table S1). There were slight differences in our study populations due to the refining of these codes over the years. In addition, Cohort-II included patients diagnosed with upper-extremity deep vein thrombosis alone. These were excluded in the present analyses due to important differences in the natural history of upper-extremity and lower-extremity deep vein thrombosis.^{16–17}

Patients were classified as either ‘first-time’ if the index event was a first-time episode, or as ‘recurrent’ at index visit if the patient had a prior episode of venous thromboembolism noted in their medical records.

Data Analysis

Annual event rates of venous thromboembolism are reported per 100,000 population. The number of first-time episodes served as the numerator for calculation of event rates of first-time venous thromboembolism (incidence rate), while the number of recurrent episodes served as the numerator for calculation of the event rates of recurrent venous thromboembolism. The 1985 United States (US) Census data of the WMSA ($n=379,953$) were used as the denominator for calculation of 1985–1989 annual crude event rates and 2000 Census data of the WMSA ($n=477,598$) were used as the denominator for calculation of 1999–2009 annual crude event rates.^{12, 14} These crude rates were used to calculate age- and sex-adjusted rates by the direct adjustment method.¹⁸ Since the WMSA population was approximately 90% white during the years under study, the age and sex distribution of the 2000 United States white (reference) population was used to calculate age- and sex-adjusted rates.¹⁹ Confidence interval (CI) estimates were based on the Poisson distribution. Trends in rates during the years under study were assessed by Poisson regression. Annual case counts were modeled using the SAS procedure GENMOD with a logarithmic link function and a log (population) offset term. A main effects model included a term for sex, age group (<40, 40–49, 50–59, 60–69, 70–79, 80 years), and study period. Separate models were constructed for episodes of first-time or recurrent venous thromboembolism, overall, and separated into pulmonary embolism (with or without deep vein thrombosis) and deep vein thrombosis alone.

Patient characteristics and diagnostic tests are reported as frequencies and percentages for categorical variables, and as means (standard deviations) or medians (interquartile ranges) for continuous variables. The Cochran-Armitage tests and linear regression models were used to test for linear trends over time among categorical variables and continuous variables, respectively. Comparison of the 2009 cohort with the 1985/86 cohort was performed using the chi-square or Fisher’s exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC) and statistical significance level was pre-specified as $\alpha=.05$ (two-sided).

RESULTS

During the study period (1985–2009), 5487 WMSA residents were diagnosed with acute venous thromboembolism (1235 from Cohort-I, 4252 from Cohort-II). After excluding 462 (10.9%) patients diagnosed with upper-extremity deep vein thrombosis alone in Cohort-II, 5025 patients with a diagnosis of acute pulmonary embolism or lower-extremity deep vein thrombosis alone were examined in the present analyses. This included 3887 (77.4%) first-time venous thromboembolism and 1138 (22.6%) recurrent venous thromboembolism. Increases in the proportion of first-time venous thromboembolism were observed over time from approximately two-thirds in the initial cohort to nearly 80% in the 2009 cohort (trend $P<.001$, Table 1).

Patient Characteristics at Index Visit

Among the 5025 patients diagnosed with venous thromboembolism, 46% were men, 95% were white, and mean age was 64.6 ± 17.8 years. Patients diagnosed with first-time venous thromboembolism tended to be younger and include an increasing proportion of ethnic minorities over the study period, but no changes were apparent in the recurrent venous thromboembolism group (Table 1). Increases in body mass index and diabetes, with a decline in the frequency of prior congestive heart failure, stroke, and malignancy, were observed in patients with first-time and recurrent venous thromboembolism. Among patients with first-time venous thromboembolism, there was a decrease in the proportion who had recent surgery, trauma, or major fracture.

The proportion of patients with community-acquired venous thromboembolism remained approximately 80% over time among patients presenting with first-time venous thromboembolism, but decreased from approximately 91% to 78% among those diagnosed with recurrent venous thromboembolism at the time of their index visit (trend $P=.001$). Overall, the proportion of patients admitted to the hospital for treatment of venous thromboembolism, or who developed index venous thromboembolism during hospitalization for another diagnosis, decreased from 100% to approximately 70% during the years under study. Among hospitalized patients, the mean length of stay during the index hospitalization decreased markedly over time in all patient groups.

Annual Event Rates

Among residents of the WMSA during the period 1985 to 2009, the overall age- and sex-adjusted annual event rate (per 100,000) was 108 (95% CI, 98 to 118) for first-time venous thromboembolism and 34 (95% CI, 28 to 40) for recurrent venous thromboembolism. Further stratifying venous thromboembolism into pulmonary embolism and deep vein thrombosis alone, the overall age- and sex-adjusted annual event rate (per 100,000) was 41 (95% CI, 35 to 47) for first-time pulmonary embolism, 66 (95% CI, 59 to 74) for first-time deep vein thrombosis alone, 9.6 (95% CI, 6.6–12.6) for recurrent pulmonary embolism, and 25 (95% CI, 20 to 29) for recurrent deep vein thrombosis alone.

There were increases over time in the age- and sex-adjusted annual event rates of first-time venous thromboembolism from 73/100,000 to 133/100,000 ($P<.001$, Figure 1A). Poisson

regression indicated an approximate 40% increase in first-time venous thromboembolism from 1985 to 2001, which remained essentially unchanged in the early 2000s, followed by an additional 50% increase by 2009 (Table 2). Although the pattern of first-time venous thromboembolism observed in WMSA between the late 1980s and early 2000s was similar in pulmonary embolism and deep vein thrombosis alone groups, the increasing trend in the late 2000s predominantly reflected an increase in the age- and sex-adjusted annual event rate of first-time pulmonary embolism, which increased from 35/100,000 in 2003 to 65/100,000 in 2009 ($P<.001$, Figure 1A).

Trends in the age- and sex-adjusted annual event rates of recurrent venous thromboembolism were U-shaped (Figure 1B). Poisson regression indicated an approximate 40% decrease in the event rates of recurrent venous thromboembolism between the mid-1980s and 1999, which remained relatively unchanged in the early 2000s, then increased in the late 2000s (Table 2). Similar trends were found for those with pulmonary embolism and deep vein thrombosis alone (Figure 1B).

Crude and adjusted annual event rates for each study period, as well as by venous thromboembolism type, are shown in Table 2. These rates increased markedly with age regardless of venous thromboembolism type, sex, or study period (Table S2).

Objective Diagnostic Tests

The proportion of patients undergoing at least one objective (either invasive or non-invasive) diagnostic test rose, with rates of non-invasive testing increasing from 60–70% in 1985/86 to nearly 100% in 2009, while rates of invasive testing plunged from over 50% to near zero (Table 3). In particular, there was a marked increase in the use of computed tomography and magnetic resonance imaging scans in the late 2000s (Table 3).

DISCUSSION

The Worcester venous thromboembolism study provides a unique opportunity to examine 25-year trends in the magnitude, characteristics, and diagnostic workup for venous thromboembolism from the perspective of a well-characterized population. The disease burden from venous thromboembolism in this central Massachusetts population remains high, with a trend towards increasing annual event rates as well as substantial changes in patient characteristics and methods used to diagnose venous thromboembolism between 1985 and 2009.

Disease Burden

The age- and sex-adjusted annual event rates of clinically recognized acute first-time and recurrent venous thromboembolism was 142/100,000 during the entire study period, increasing from 112/100,000 in 1985/86 to 168/100,000 in 2009. It is higher than the incidence of the leading two cancers (126/100,000 for prostate cancer and 124/100,000 for breast cancer) and >15 times higher than the incidence rate of HIV (8.3/100,000) in white Americans.²⁰ The age- and sex-adjusted annual event rate of clinically recognized acute pulmonary embolism was 78/100,000 in 2009, nearly equivalent to the annual incidence of

ischemic stroke (88/100,000) in white individuals reported by the American Heart Association during that period.¹⁸

With increased long-term morbidity and functional disability, and high rates of recurrence and mortality among venous thromboembolism patients,¹ this disorder remains a major national health problem with a substantial disease burden.

Time Trends in Occurrence

Between 1985 and 2009, the annual event rates of first-time venous thromboembolism nearly doubled, and first-time pulmonary embolism nearly tripled, with inconsistent patterns noted among patients with recurrent venous thromboembolism.

Our study is the first population-based surveillance project of venous thromboembolism to provide data about trends in annual event rates of first-time and recurrent venous thromboembolism between 1985 and 2009. Data from the Rochester Epidemiology Project (REP), the study with the most similar design to ours, indicated a 23% increase in age- and sex-adjusted annual event rate of first-time venous thromboembolism from 96/100,000 in 1986–1990 to 118/100,000 in 1991 to 1997.^{19, 21} These results are similar to the 30% increase in the age- and sex-adjusted annual event rate of first-time venous thromboembolism observed in our study between 1985 and 1999. A study based on the US Nationwide Inpatient Sample demonstrated that the number of patients with first-time and recurrent pulmonary embolism discharged from US acute care hospitals approximately doubled between 1998 and 2005,²² consistent with our findings. A retrospective study based on estimates derived from commercial insurance and Medicare databases of insured US residents observed a 33% increase in annual event rates of first-time and recurrent venous thromboembolism between 2002 and 2006.²³ This increase was larger than the approximate 20% increase in the age- and sex-adjusted annual event rates of first-time and recurrent venous thromboembolism observed in the present study (from 131/100,000 in 2001 to 154/100,000 in 2007). These results, based on commercial insurance and Medicare databases, may be limited due to their reliance on administrative databases without actual chart review and independent diagnostic validation.

Both the REP and our study indicated that the frequency of venous thromboembolism increased markedly with age regardless of study year, venous thromboembolism type, or sex. Given the aging of the United States population,²⁴ the projected disease burden of venous thromboembolism is expected to more than double between 2006 and 2050.²³

Possible Contributory Factors to Observed Trends

Observed increases in the frequency of venous thromboembolism during the study period are likely to be multifactorial. First, the use of one or more non-invasive diagnostic methods for the detection of venous thromboembolism increased from approximately two-thirds of patients in 1985 to nearly all in 2009. In particular, the introduction of computed tomography pulmonary angiography (CTPA) closely parallels the observed increases in the annual event rate of first-time and recurrent pulmonary embolism observed in our study. The proportion of pulmonary embolism patients who underwent a CTPA test increased from approximately 25% in 1999 to 85% in 2009. During this period, the annual event rate of

first-time and recurrent pulmonary embolism more than doubled. A time-trend analysis using the Nationwide Inpatient Sample and Multiple Cause-of-Death databases demonstrated that the introduction of CTPA was associated with changes consistent with a rising frequency of pulmonary embolism in the US²⁵. Clearly we are detecting more cases of venous thromboembolism during recent years than were detected (or were detectable) in the decades before the introduction of newer technology. A more difficult question to address is how much of this increase represents small, clinically insignificant pulmonary embolisms? Following the introduction of high-resolution multiple-detector CTPA, systematic reviews and meta-analyses have suggested an increase in the diagnosis of subsegmental pulmonary embolisms of unclear clinical significance through the use of these newer testing modalities.²⁶ Because most of these subsegmental pulmonary embolisms are treated, their importance remains a key healthcare and resource dilemma. Further study of this issue is warranted.

With expanded access to higher resolution diagnostic imaging, a growing awareness of venous thromboembolism as an important public-health problem may have led clinicians to refer additional patients for evaluation.²⁷ Our findings indicate that the proportion of patients who received any form of objective diagnostic testing has increased over time.

In addition to changes in the diagnosis of venous thromboembolism, the increases in annual event rates of venous thromboembolism observed in WMSA residents could also be related to changes in population characteristics over time. As the US population ages and becomes less active and more obese,^{20, 24} it may lead to further increases in risk of developing venous thromboembolism.

Although the development and implementation of evidence-based practice guidelines for venous thromboembolism prevention and treatment may have reduced the annual event rate of venous thromboembolism among ‘high-risk’ patients, including those with a recent history of a surgical procedure, pregnancy, trauma, fracture, and hospitalization,²⁸ this would not be expected to impact patients without obvious recent provocations who would be less likely to have received enhanced venous thromboembolism prophylaxis compared with high-risk patients.

Our findings demonstrate that the proportion of patients with community-acquired first-time venous thromboembolism has remained relatively constant, at approximately 80%, during the 25-year period under study. A prior publication from our study suggests that approximately 40% of patients with community-acquired venous thromboembolism had a hospitalization or surgery in the 3 months before their index visit.²⁹ Further work identifying and providing prophylaxis to high-risk patients being discharged from hospital is needed. With respect to the remaining 60% (with unprovoked venous thromboembolism), research aimed at better understanding such patients by risk and identifying possible “minor” triggers for a venous thromboembolism event may provide additional opportunities for prophylaxis.

Interestingly, although the annual event rate of recurrent venous thromboembolism remained relatively unchanged between 1985 and 2009, the trend was U-shaped. The decreasing trend observed between the late 1980s to 1999 could be related to development of improved

treatment strategies.^{30–36} However, given increases in the annual event rates of first-time venous thromboembolism and high recurrence of this thromboembolic disorder,^{1, 7} it was not surprising that the annual event rates of recurrent venous thromboembolism also increased in residents of the WMSA during the late 2000s.

Study Strengths and Limitations

The Worcester venous thromboembolism study employed rigorous population-based surveillance methods to describe the clinical epidemiology of acute venous thromboembolism in the WMSA. Although we conducted broad screening for cases of venous thromboembolism using multiple databases, validated each potential case of venous thromboembolism, and performed regular chart audits, it is possible that this study may have missed some cases. Owing to low autopsy rates in the WMSA, and the limited validity of death-certificate data, only clinically recognized cases of acute venous thromboembolism were described and some cases of fatal pulmonary embolism could be missed. Further, regional differences may exist in the diagnostic workup of patients presenting with signs and symptoms of venous thromboembolism. Since the WMSA is predominantly a white population, additional population-based studies in minority and economically disadvantaged populations are needed. Owing to lack of funding, we did not collect data between 1990 and 1998, which may not provide a comprehensive view of 25-year trend between 1985 and 2009.

CONCLUSION

Despite advances in identification, prophylaxis, and treatment between 1985 and 2009, the annual event rate of venous thromboembolism has increased and remains high. While these increases may be partially due to increased sensitivity of diagnostic methods, especially for pulmonary embolism, it may also imply that current prevention and treatment strategies are less than optimal.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Significance

- Despite the substantial evolution in methods for venous thromboembolism prevention, diagnosis, and treatment between 1985 and 2009, the disease burden from venous thromboembolism remains high.
- Observed increases in the annual event rates of venous thromboembolism may have been due partially to improved detection of venous thromboembolism, especially pulmonary embolism, with more sensitive imaging modalities.
- Increases in the incidence of pulmonary embolism may be the result of small emboli detected by computed tomography.

Figure 1.

Age- and sex-adjusted annual event rates of (a) first-time and (b) recurrent clinical recognized acute venous thromboembolism among residents of Worcester, Massachusetts, metropolitan statistical area (1985 to 2009).

Table 1
Characteristics of patients with venous thromboembolism in the Worcester venous thromboembolism study (1985–2009)

	Study year								P value
	1985/1986 (n=617)	1988/1989 (n=618)	1999 (n=539)	2001 (n=597)	2003 (n=554)	2005 (n=608)	2007 (n=698)	2009 (n=794)	
First-time venous thromboembolism at index visit, n (% of total venous thromboembolism)	405 (65.6)	442 (71.5)	435 (80.7)	482 (82.4)	466 (84.1)	482 (79.3)	542 (77.7)	633 (79.7)	<.001
Demographic characteristics									
Age (years)									.04
Mean (standard deviation)	65.9 (17.2)	66.4 (17.4)	66.4 (17.7)	65.8 (17.3)	63.0 (17.9)	62.7 (18.9)	65.0 (18.1)	63.7 (17.8)	
Median (interquartile range)	69 (60–78)	70 (60–78)	72 (54–80)	69 (54–81)	65 (50–78)	65 (48–79)	68 (52–80)	65 (50–80)	
Men (%)	48.6	45.5	43.4	41.9	46.8	41.3	47.6	44.6	.34
White (%)	97.5	98.2	95.4	93.5	93.6	94.8	95.7	92.5	.001
Recent* medical characteristics (%)									
Body mass index class									
<25 kg/m ²	42.1	44.2	35.3	32.9	26.0	36.5	28.9	26.9	<.001
25–30 kg/m ²	35.1	28.8	27.4	31.4	33.3	28.4	35.2	29.5	.80
>30 kg/m ²	22.8	27.1	37.3	35.6	4.7	35.1	35.9	43.6	<.001
Congestive heart failure	20.2	11.5	13.1	14.9	11.2	10.0	9.2	7.4	<.001
Myocardial infarction	4.9	3.4	5.1	7.3	6.4	4.1	3.0	2.5	.04
Stroke	4.2	6.6	6.4	7.1	5.6	2.7	2.2	2.2	.07
Chronic obstructive pulmonary disease	23.2	15.8	17.0	21.4	16.7	21.8	24.7	23.7	.86
Diabetes	14.3	16.5	17.0	22.4	18.0	17.2	23.4	18.8	.06
Malignancy	30.4	23.3	19.3	19.9	12.7	15.6	16.8	19.0	<.001
Trauma/fracture	12.8	13.8	17.7	21.0	13.5	9.8	8.9	9.5	.09
Hormone replacement therapy/oral contraceptives [†]	4.3	4.6	21.1	21.4	14.9	10.6	7.4	10.9	.01
Post partum [‡]	3.8	1.7	2.4	1.1	1.2	2.5	1.1	1.4	.07
Any surgery, including index admission	34.6	30.5	29.2	30.5	25.8	28.2	23.2	22.7	<.001
Venous thromboembolism characteristics (%)									
Type of venous thromboembolism event									
Pulmonary embolism alone	24.2	22.2	15.9	20.5	18.9	28.4	29.9	28.8	<.001
.11									

	Study year							P value	
	1985/1986 (n=617)	1988/1989 (n=618)	1999 (n=539)	2001 (n=597)	2003 (n=554)	2005 (n=608)	2007 (n=698)	2009 (n=794)	Trend test 1985/86 vs 2009
Pulmonary embolism and deep vein thrombosis	8.2	6.6	15.6	14.7	15.2	18.9	19.6	19.7	<.001
Lower-extremity deep vein thrombosis alone	67.7	71.3	68.5	64.7	65.9	52.7	50.5	51.5	<.001
Community acquired	78.0	80.1	73.6	75.1	75.8	78.8	79.5	77.1	.73
Hospital encounter,									
Admitted to hospital [§] (%)	100	100	77.7	77.2	70.8	74.3	73.1	71.1	<.001
If admitted, length of stay, days									<.001
Mean (standard deviation)	15.3 (24.1)	15.1 (15.5)	9.0 (10.0)	10.1 (11.5)	9.6 (10.8)	8.5 (11.0)	7.2 (8.6)	6.9 (8.0)	
Median (interquartile range)	10 (8–19)	10 (7–16)	6 (4–9)	6 (4–10)	6 (4–10)	5 (3–9)	5 (3–8)	5 (3–8)	
Recurrent venous thromboembolism at index visit, n (% of total venous thromboembolism)	212 (34.4)	176 (28.5)	104 (19.3)	115 (19.3)	88 (15.9)	126 (20.7)	156 (22.4)	161 (20.3)	<.001
Patient characteristics									
Age (years)									.10
Mean (standard deviation)	62.6 (17.3)	61.1 (19.0)	64.1 (16.6)	64.7 (17.2)	65.4 (17.7)	63.8 (18.0)	66.9 (15.5)	64.9 (16.8)	.17
Median (interquartile range)	66 (49–75)	67 (48–75)	69 (51–77)	67 (51–80)	71 (54–79)	64 (49–80)	69 (57–80)	67 (53–79)	
Men (%)	45.8	55.1	47.1	47.0	50.0	48.4	50.0	51.6	.83
White (%)	96.2	97.2	90.7	93.6	95.4	96.0	94.7	92.4	.10
Recent [*] medical characteristics (%)									
Body mass index class									
<25 kg/m ²	39.0	38.6	33.8	30.9	28.1	34.8	28.9	27.6	.01
25–30 kg/m ²	30.8	36.2	36.4	35.8	35.1	28.1	31.6	30.6	.60
>30 kg/m ²	30.1	25.2	29.9	33.3	36.8	37.1	39.5	41.8	.002
Congestive heart failure	18.9	9.7	8.7	13.9	6.8	4.0	10.7	8.1	<.001
Myocardial infarction	2.8	0.6	3.8	3.5	6.8	1.6	3.8	3.7	.14
Stroke	4.2	1.7	9.6	5.2	6.8	1.6	0.6	1.2	.26
Chronic obstructive pulmonary disease	25.9	19.3	19.2	20.9	10.2	26.2	32.7	29.8	.13
Diabetes	15.6	11.4	17.3	16.5	13.6	19.0	19.2	26.7	.003
Malignancy	25.9	25.0	11.5	13.9	9.1	15.1	19.2	16.8	<.001
Trauma/fracture	4.2	5.1	12.5	12.2	12.5	8.7	4.5	8.1	.07
Hormone replacement therapy/oral contraceptives [†]	3.5	6.3	36.4	26.2	6.8	9.2	2.6	6.4	.32

	Study year								P value	
	1985/1986 (n=617)	1988/1989 (n=618)	1999 (n=539)	2001 (n=597)	2003 (n=554)	2005 (n=608)	2007 (n=698)	2009 (n=794)	Trend test	1985/86 vs 2009
Post partum [†]	2.6	0	0	0	0	0	0	0	.01	.27
Any surgery, including index admission	15.6	16.5	17.3	15.7	10.2	21.4	16.7	17.4	.61	.64
Venous thromboembolism characteristics (%)										
Type of venous thromboembolism event										
Pulmonary embolism alone	16.5	15.3	12.5	20.0	13.6	16.7	17.3	23.6	.10	.09
Pulmonary embolism and deep vein thrombosis	9.4	10.2	13.5	9.6	8.0	11.1	12.8	13.7	.20	.20
Lower-extremity deep vein thrombosis alone	74.1	74.4	74.0	70.4	78.4	72.2	69.9	62.7	.02	.02
Community acquired	91.0	91.5	86.5	85.2	86.4	82.5	82.7	77.6	<.001	<.001
Hospital encounter [§] (%)										
Admitted to hospital	100	100	78.8	63.5	68.2	70.6	65.4	73.3	<.001	<.001
If admitted, length of stay, days									<.001	<.001
Mean (standard deviation)	11.9 (11.3)	10.9 (7.8)	7.4 (8.4)	7.0 (9.3)	6.4 (7.0)	6.7 (5.9)	9.5 (10.4)	6.3 (8.0)		
Median (interquartile range)	9 (7–13)	9 (7–13)	5 (4–8)	5 (3–8)	4 (2–7)	5 (3–8)	6 (3–10)	3 (2–7)		

* Recent defined as <6 months in 1980s cohort, <3 months in 1999–2007 cohort.

[†] Among women.

[§] Reflecting the standard care for the treatment of acute venous thromboembolism in 1980s, cohorts 85/86 and 88/89 included only inpatients diagnosed with acute venous thromboembolism.

Table 2

Annual event rates (per 100,000) of clinically recognized acute venous thromboembolism among Worcester metropolitan statistical area residents (1985–2009)

	Rate (95% confidence interval)						
	1985/1986	1988/1989	1999	2001	2003	2005	2007
First-time venous thromboembolism at index visit							
Crude	71 (63–80)	78 (69–87)	91 (83–100)	101 (92–110)	98 (89–107)	101 (92–110)	113 (104–123)
Adjusted*	73 (64–82)	81 (72–91)	95 (86–104)	106 (96–115)	103 (94–112)	105 (95–114)	119 (109–129)
Incidence rate ratio $\ddagger$	Reference group	1.1 (0.9–1.3)	1.3 (1.1–1.5)	1.4 (1.2–1.6)	1.4 (1.2–1.6)	1.4 (1.2–1.6)	1.6 (1.4–1.8)
First-time pulmonary embolism $\pm$ deep vein thrombosis at index visit							
Crude	23 (19–28)	22 (18–27)	29 (24–34)	36 (31–41)	33 (28–39)	48 (42–54)	56 (50–63)
Adjusted*	24 (19–29)	23 (18–28)	30 (25–35)	37 (32–43)	35 (30–41)	50 (44–57)	59 (52–66)
Incidence rate ratio $\ddagger$	Reference group	1.0 (0.7–1.3)	1.2 (1.0–1.6)	1.5 (1.2–2.0)	1.4 (1.1–1.9)	2.1 (1.6–2.7)	2.4 (1.9–3.1)
First-time deep vein thrombosis alone at index							
Crude	48 (41–55)	55 (48–63)	62 (56–70)	65 (58–73)	64 (57–72)	53 (47–60)	57 (51–64)
Adjusted*	49 (42–56)	58 (50–66)	65 (58–72)	68 (61–76)	68 (60–75)	54 (48–61)	60 (53–67)
Incidence rate ratio $\ddagger$	Reference group	1.1 (0.9–1.4)	1.3 (1.1–1.6)	1.4 (1.1–1.6)	1.3 (1.1–1.6)	1.1 (0.9–1.3)	1.2 (1.0–1.4)
Recurrent venous thromboembolism at index visit							
Crude	37 (31–44)	31 (26–37)	22 (18–26)	24 (20–29)	18 (15–23)	26 (22–31)	33 (28–38)
Adjusted*	39 (32–45)	32 (27–38)	23 (19–28)	25 (21–30)	19 (15–23)	28 (23–32)	35 (29–40)
Incidence rate ratio $\ddagger$	Reference group	0.8 (0.6–1.1)	0.6 (0.5–0.8)	0.6 (0.5–0.8)	0.5 (0.4–0.6)	0.7 (0.6–0.9)	0.9 (0.7–1.1)
Recurrent pulmonary embolism $\pm$ deep vein thrombosis at index visit							
Crude	10 (7–13)	8 (5–11)	6 (4–8)	7 (5–10)	4 (2–6)	7 (5–10)	10 (7–13)
Adjusted*	10 (7–13)	8 (5–11)	6 (4–8)	8 (5–10)	4 (2–6)	8 (5–10)	11 (8–14)
Incidence rate ratio $\ddagger$	Reference group	0.8 (0.5–1.3)	0.6 (0.4–1.0)	0.7 (0.5–1.2)	0.4 (0.2–0.7)	0.8 (0.5–1.2)	1.0 (0.7–1.6)
Recurrent deep vein thrombosis alone at index visit							
Crude	28 (23–33)	23 (19–28)	16 (13–20)	17 (14–21)	14 (11–18)	19 (15–23)	23 (19–27)

Rate (95% confidence interval)									
	1985/1986	1988/1989	1999	2001	2003	2005	2007	2009	
Adjusted*	29 (23–34)	24 (19–29)	17 (13–21)	18 (14–22)	15 (12–19)	20 (16–24)	24 (20–29)	21 (17–25)	
Incidence rate ratio†	Reference group	0.8 (0.6–1.1)	0.6 (0.4–0.8)	0.6 (0.5–0.8)	0.5 (0.4–0.7)	0.7 (0.5–0.9)	0.8 (0.6–1.1)	0.8 (0.6–1.0)	

* Directly age- and sex-adjusted to the 2000 United States white population.

† Based on Poisson regression adjusted by age and sex.

Table 3
Diagnostic methods for venous thromboembolism: the Worcester venous thromboembolism study (1985–2009)

	Study year								P value	
	1985/1986 (n=617)	1988/1989 (n=618)	1999 (n=539)	2001 (n=597)	2003 (n=554)	2005 (n=608)	2007 (n=698)	2009 (n=794)	Trend Test	1985/86 vs 2009
First-time event at index, n (%)	n=405	n=442	n=435	n=482	n=466	n=482	n=542	n=633		
Any invasive* diagnostic method	237 (58.5)	206 (46.6)	6 (1.4)	18 (3.7)	9 (1.9)	14 (2.9)	11 (2.0)	15 (2.4)	<.001	<.001
Any non-invasive diagnostic method	285 (70.4)	335 (75.8)	406 (93.3)	456 (94.6)	453 (97.2)	477 (99.0)	535 (98.7)	615 (97.2)	<.001	<.001
Diagnostic tests in patients with deep vein thrombosis (%)	n=307	n=344	n=366	n=383	n=378	n=345	n=380	n=451		
Venogram	67.8	54.9	0.5	1.6	0.8	2.0	1.1	0.7	<.001	<.001
Impedance plethysnography	57.7	53.2	0	0	0	0	0	0	<.001	<.001
Duplex/ultrasound scan	0.3	36.3	92.9	91.6	94.4	93.0	91.3	97.8	<.001	<.001
Computed tomography	0	0	3.3	7.0	6.9	4.9	10.3	2.9	<.001	.003
Magnetic resonance imaging	0	0	0	0	0.3	7.8	9.2	0.7	<.001	.28
Any of above tests	94.8	96.8	95.4	95.6	97.6	99.4	100	99.1	<.001	<.001
Diagnostic tests in patients with pulmonary embolism (%)	n=131	n=127	n=137	n=170	n=159	n=228	n=268	n=307		
Pulmonary angiogram	16.8	11.0	2.2	2.4	2.5	2.6	2.6	3.9	<.001	<.001
Lung scan	80.9	88.2	59.1	40.0	19.5	24.1	11.2	7.5	<.001	<.001
Spiral computed tomography	0	0	24.8	60.6	79.2	80.7	86.9	87.3	<.001	<.001
Magnetic resonance imaging	0	0	0	0	0	0.4	0	0.3	.33	1.0
Any of above tests	90.1	93.7	92.7	95.3	97.5	98.7	97.8	96.4	<.001	.008
Recurrent event at index, n (%)	n=212	n=176	n=104	n=115	n=88	n=126	n=156	n=161		
Any invasive* diagnostic method	108 (50.9)	63 (35.8)	0	1 (0.9)	1 (1.1)	6 (4.8)	6 (3.8)	1 (0.6)	<.001	<.001
Any non-invasive diagnostic method	126 (59.4)	122 (69.3)	97 (93.3)	107 (93.0)	85 (96.6)	124 (98.4)	153 (98.1)	158 (98.1)	<.001	<.001
Diagnostic tests in patients with deep vein thrombosis (%)	n=177	n=149	n=91	n=92	n=76	n=105	n=129	n=123		
Venogram	49.7	39.6	0	1.1	1.3	3.8	2.3	0	<.001	<.001
Impedance plethysnography	47.5	49.7	0	0	0	0	0	0	<.001	<.001
Duplex/ultrasound scan	0	32.2	94.5	92.4	93.4	96.2	89.1	97.6	<.001	<.001
Computed tomography	0	0	1.1	1.1	6.6	2.9	7.0	4.1	<.001	.01
Magnetic resonance imaging	0	0	0	0	0	6.7	11.6	4.1	<.001	.01

	Study year								P value		
	1985/1986 (n=617)	1988/1989 (n=618)	1999 (n=539)	2001 (n=597)	2003 (n=554)	2005 (n=608)	2007 (n=698)	2009 (n=794)	Trend Test	1985/86 vs 2009	
Any of above tests	83.6	87.9	94.5	94.6	98.7	99.0	99.2	99.2	<.001	<.001	
Diagnostic tests in patients with pulmonary embolism (%)	n=55	n=45	n=27	n=34	n=19	n=35	n=47	n=60			
Pulmonary angiogram	12.7	4.4	0	0	0	2.9	6.4	0	.004	.005	
Lung scan	65.5	88.9	66.7	44.1	31.6	22.9	8.5	13.3	<.001	<.001	
Spiral computed tomography	0	0	25.9	58.8	63.2	74.3	85.1	78.3	<.001	<.001	
Magnetic resonance imaging	0	0	0	0	0	0	0	0	Not applicable	Not applicable	
Any of above tests	76.4	95.6	92.6	94.1	89.5	97.1	97.9	96.7	.001	.001	

* Invasive tests including venogram and pulmonary angiogram.