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Venous Thromboembolism in Patients with Diabetes Mellitus

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Abstract

PURPOSE—The majority of epidemiological studies demonstrate an increased risk of venous thromboembolism among diabetic patients. Our aim was to compare clinical characteristics, prophylaxis, treatment, and outcomes of venous thromboembolism in patients with and without previously diagnosed diabetes.

METHODS—We studied diabetic patients in the population-based Worcester Venous Thromboembolism Study of 2488 consecutive patients with validated venous thromboembolism.

RESULTS—Of 2488 venous thromboembolism patients, 476 (19.1%) had a clinical history of diabetes. Thromboprophylaxis was omitted in more than one third of diabetic patients who had been hospitalized for non-venous-thromboembolism-related illness or had undergone major surgery within 3 months before diagnosis. Patients with diabetes were more likely than nondiabetic patients to have a complicated course after venous thromboembolism. Patients with diabetes were more likely than patients without diabetes to suffer recurrent deep vein thrombosis (14.9% vs 10.7%) and long-term major bleeding complications (16.4% vs 11.7%) (all $P = .01$). Diabetes was associated with a significant increase in the risk of recurrent deep vein thrombosis (adjusted odds ratio [AOR] 1.74; 95% confidence interval [CI], 1.21–2.51). Aspirin therapy at discharge (AOR 1.59; 95% CI, 1.1–2.3) and chronic kidney disease (AOR 2.19; 95% CI, 1.44–3.35) were independent predictors of long-term major bleeding.

CONCLUSION—Patients with diabetes who developed venous thromboembolism were more likely to suffer a complicated clinical course. Diabetes was an independent predictor of recurrent deep vein thrombosis. We observed a low rate of thromboprophylaxis in diabetic patients. Further studies should focus on venous thromboembolism prevention in this vulnerable population.

Keywords

Deep vein thrombosis; Diabetes mellitus; Prophylaxis; Pulmonary embolism; Treatment; Venous thromboembolism

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Venous thromboembolism shares many risk factors with atherosclerotic cardiovascular disease, including obesity, hypertension, dyslipidemia, smoking, and diabetes.¹ The age-adjusted incidence of diabetes has increased sharply in the last 2 decades to 9.1 per 1000 in the US population aged 18 years and older.² While data linking diabetes to the development of venous thromboembolism have been inconsistent,^{3,4} the majority of epidemiological studies demonstrate an increased risk of deep vein thrombosis and pulmonary embolism among diabetic patients.^{5–8} Based on data from 92 million diabetic patients in the US National Hospital Discharge Survey, the relative risk of venous thromboembolism is greatest in younger patients with diabetes.⁶

The increased risk of venous thromboembolism associated with diabetes ranges from 40% in a large prospective cohort from the US⁵ to 50% in a meta-analysis of more than 63,000 patients.⁸ The risk of venous thromboembolism appears to be elevated in both type 1 and type 2 diabetic patients.⁷ Increased thrombin generation and higher concentration of procoagulant cell-derived circulating microparticles in patients with type 2 diabetes suggest that hypercoagulability may play an important pathogenic role in the increased frequency of venous thromboembolism.⁹

Using data from a population-based study of central Massachusetts residents with independently confirmed venous thromboembolism, we compared the clinical characteristics, use of prophylaxis, treatment strategies, and outcomes of 476 patients with a clinical diagnosis of diabetes with those of 2012 patients without diabetes in the Worcester Venous Thromboembolism Study.

METHODS

Patient Population

Lists of eligible patients were generated from health care system encounters in which any of 34 International Classification of Diseases, 9th Revision diagnosis codes consistent with venous thromboembolism were used in 1999, 2001, 2003, and 2005.¹⁰ These lists were obtained from each of the 11 medical centers serving residents of the Worcester, Massachusetts metropolitan area.¹⁰ Institutional Review Board approval was obtained at all 11 study sites. Data queries included discharge diagnoses and outpatient, emergency department, radiology, and laboratory clinical encounters. The medical records of all potentially eligible patients were reviewed by dedicated nurse abstractors using prespecified criteria to validate and characterize each case of suspected venous thromboembolism.¹⁰ These criteria were adapted from an established classification scheme.^{11,12} Each potential case of venous thromboembolism was independently validated by the study project coordinator using prespecified diagnostic criteria. Each case of venous thromboembolism was classified as being either definite, probable, possible, or negative based on a modification of the classification used by Silverstein et al (Appendix).^{11,12} A definite diagnosis of deep vein thrombosis required evidence for presumed acute thrombosis by compression ultrasonography, computed tomography, magnetic resonance imaging, or venography. A definite diagnosis of pulmonary embolism required evidence for presumed new thrombosis on computed tomography or pulmonary angiography. Probable pulmonary embolism required the presence of a high-probability ventilation-perfusion lung scan. Cases of deep vein thrombosis or pulmonary embolism were classified as possible if these confirmatory tests were not performed or were indeterminate. Two of the following 3 criteria were met: the medical record indicated that the physician made a clinical diagnosis of deep vein thrombosis or pulmonary embolism; symptoms or signs of venous thromboembolism were documented; or the patient underwent therapy with anticoagulants or an inferior vena cava filter was inserted. If the classification of venous thromboembolism was not immediately clear using the specified criteria, the principal investigator (FAS)

reviewed the medical record. Only definite, probable, and possible cases were included in the present analysis. There were no exclusion criteria for entry into the registry.

Incident cases of venous thromboembolism were defined as those occurring in patients with no prior history of deep vein thrombosis or pulmonary embolism. Recurrent venous thromboembolism was defined as a new occurrence of thrombosis in a previously uninvolved vein or pulmonary artery as detected by an imaging study.

Data Collection

Data about demographic characteristics, comorbidities, risk factors, diagnosis, management, prior prophylaxis utilization, and outcomes were abstracted from inpatient and out-patient medical records. Patients with a clinical diagnosis of diabetes mellitus type 1 or type 2 were identified based on information contained in hospital and ambulatory care records and were classified as having diabetes. Data on treatment of diabetes (diet, oral hypoglycemic agent, or insulin) also were abstracted. Surgery was defined as a major operation where general or epidural anesthesia lasted 30 minutes or longer. Immobility was defined as limited ambulation, restricted activity of bed-to-chair or bed-to-bathroom, or complete bed rest based on medical record documentation. Clinical characteristics were defined as “recent” if occurring or active within 3 months before venous thromboembolism diagnosis.

Major bleeding for study years 1999, 2001, and 2003 was defined as any episode of bleeding requiring transfusion or resulting in hospitalization (or prolongation of hospitalization), stroke, myocardial infarction, or death. To be consistent with International Society of Thrombosis and Hemostasis criteria,¹³ our definition was revised for the 2005 patient cohort. Major bleeding was defined as clinically overt bleeding that: resulted in death; was at a critical site (intracranial, intraocular, retroperitoneal, intraarticular, pericardial, or muscular with compartment syndrome; required transfusion of at least 2 units of packed red blood cells; or resulted in a hemoglobin decrease of at least 20 g/L.

Data about thromboprophylaxis utilization were obtained for patients hospitalized for any non-venous-thromboembolism-related disorder or for major surgery within the 3 months before the diagnosis of deep vein thrombosis or pulmonary embolism. This information was abstracted from medical records at the same time as data about the incident venous thromboembolism event. Medical records from other area hospitals were reviewed in case prior hospitalization was at an institution other than that of the index venous thromboembolism. First recurrence of venous thromboembolism or a major bleeding event was determined through review of medical records at the same hospital as the index event and screening of medical records from the other participating medical centers. Data about all-cause mortality were obtained through review of hospital records and death certificates at the Massachusetts Division of Vital Statistics. Median follow-up was 992 days for long-term outcomes.

Statistical Methods

Means, medians, and frequency distributions were calculated for continuous variables. Differences in the distribution of demographic characteristics, comorbidities, risk factors, diagnosis, management strategies, prophylaxis, and outcomes between patients with and without diabetes were examined using the chi-squared or Fisher’s exact test for categorical variables and *t*-test for continuous variables. Cumulative incidence rates of venous thromboembolism recurrence, major bleeding, and all-cause mortality were estimated using the life-table method, with differences in the frequency of these outcomes compared between patients with and without diabetes using the log-rank test. All statistical tests were 2-tailed, and a *P*-value of <.05 was considered to be statistically significant.

Cox regression analysis was utilized to evaluate whether a clinical diagnosis of diabetes was associated with an increased risk of recurrent deep vein thrombosis and long-term major bleeding while controlling for several potentially confounding prognostic factors. Variables included in the regression model for recurrent deep vein thrombosis were selected based on the results of univariate analysis and a priori knowledge and included age, sex, body mass index, medical history (history of diabetes, heart failure, indwelling central venous catheter, and chronic kidney disease), recent immobility, and type of venous thromboembolism on presentation (unprovoked vs provoked). Variables included in the regression model for long-term major bleeding were selected based on the results of univariate analysis and a priori knowledge and included age, sex, body mass index, history of diabetes, history of chronic kidney disease, and aspirin therapy at discharge. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Baseline Characteristics

Patients with diabetes who developed venous thromboembolism were significantly older than nondiabetic patients (mean age 68.2 years vs 62.8 years) (Table 1). Patients with diabetes were more likely to have developed venous thromboembolism during hospitalization for a non-venous-thromboembolism-related condition (38.2% vs 25.8%, $P < .001$). Diabetic patients with venous thromboembolism had a longer mean duration of hospitalization than those without diabetes (13.8 days vs 9.7 days, $P = .001$).

Comorbidities and Risk Factors

Patients with diabetes and venous thromboembolism were more likely than patients without diabetes to have comorbid conditions of immobility >48 hours, acute infectious illness, heart failure, chronic lung disease, ischemic heart disease, cerebrovascular disease, and chronic kidney disease (Table 2). Patients with diabetes also were significantly more likely to have an indwelling central venous catheter than nondiabetic patients (28.8% vs 16.1%). Diabetic patients were more likely to have been discharged from the intensive care unit within the 3 months before venous thromboembolism diagnosis than nondiabetic patients (25.6% vs 14.1%, $P < .001$).

Of the 476 diabetic patients with venous thromboembolism, 33% were receiving insulin, 45.5% were taking oral hypoglycemic drugs, and 21.5% were diet controlled.

Clinical Presentation of Venous Thromboembolism

Presenting symptoms and signs of venous thromboembolism were similar among patients with and without diabetes, with the exception being that extremity pain was less frequent, whereas loss of consciousness was more frequent in diabetic patients (Table 3). Loss of consciousness occurred exclusively in diabetic patients who suffered pulmonary embolism. Deep vein thrombosis was more frequently diagnosed in patients with diabetes (88.7% vs 85%, $P = .03$) than in those without. Unprovoked (idiopathic) venous thromboembolism was less frequent in patients with diabetes than in those without diabetes (16.6% vs 27.2%, $P < .001$). There was an increased frequency of upper extremity deep vein thrombosis in diabetic patients compared with nondiabetic patients (15.8% vs 10.9%, $P = .004$). The proportion of patients with upper extremity deep vein thrombosis and an indwelling central venous catheter was greater among those with diabetes than among nondiabetics (77.3% vs 58.9%, $P = .004$). Patients with diabetes were more likely than nondiabetic patients to be receiving aspirin at the time of venous thromboembolism diagnosis (31.9% vs 21.9%, $P < .001$).

Prophylaxis of Venous Thromboembolism

Patients with diabetes who were hospitalized for any non-venous-thromboembolism-related condition or had major surgery within the 3 months before diagnosis of deep vein thrombosis or pulmonary embolism were more likely than nondiabetic patients to have received prophylactic measures (60.4% vs 46.6%, $P < .001$) (Table 4). Patients with diabetes were more likely to have received pneumatic compression devices, subcutaneous unfractionated heparin, or intravenous unfractionated heparin.

Treatment of Venous Thromboembolism

Intravenous unfractionated heparin was the most common parenteral anticoagulant used in the initial treatment of venous thromboembolism in patients with diabetes, while low-molecular-weight heparin was most frequently used in nondiabetics (Table 5). Inferior vena cava filter placement was more common among patients with diabetes (15.6% vs 10.9%, $P = .01$). Diabetic patients were less likely to be prescribed low-molecular-weight heparin as a bridge to therapeutic anticoagulation with warfarin at discharge. In addition to antithrombotic therapy for venous thromboembolism, diabetic patients were more likely than nondiabetic patients to be prescribed aspirin at discharge (19.1% vs 11.4%, $P < .001$).

Neither low-molecular-weight heparin nor warfarin were prescribed at discharge in 24.4% of diabetic patients and 18.4% nondiabetic patients ($P = .004$). Of patients with venous thromboembolism who were not discharged on either low-molecular-weight heparin or warfarin, 34.9% of diabetics and 22.9% of nondiabetics had indwelling central venous catheters ($P = .01$) and may have had upper-extremity deep vein thrombosis that was only briefly treated. Of patients with venous thromboembolism who were not discharged on either low-molecular-weight heparin or warfarin, 6.4% of diabetics and 5.1% of nondiabetics were discharged on unfractionated heparin ($P = .59$), and 0.9% of diabetics and 1.1% of nondiabetics were discharged on an anticoagulant other than unfractionated heparin, low-molecular-weight heparin, or warfarin ($P = .85$).

Outcomes

Patients with diabetes were more likely than nondiabetic patients to have a complicated course after venous thromboembolism (Table 6). Patients with diabetes were more likely than patients without diabetes to have developed a recurrent deep vein thrombosis (14.9% vs 10.7%, $P = .01$) and long-term major bleeding complications (16.4% vs 11.7%, $P = .01$). Of patients with recurrent deep vein thrombosis, 26.8% of diabetics and 26.9% of nondiabetics were discharged on neither low-molecular-weight heparin nor warfarin ($P = .99$). The median times to recurrent deep vein thrombosis, recurrent pulmonary embolism, and major bleeding for the total study population were 94 days, 176 days, and 16 days, respectively. The median times to recurrent deep vein thrombosis, recurrent pulmonary embolism, and major bleeding were 86 days, 328 days, and 16 days, respectively, for diabetic patients and 95 days, 134 days, and 18 days, respectively, for nondiabetic patients ($P > .05$ for all comparisons).

After adjusting for potentially confounding prognostic variables, only history of diabetes was associated with a significant increase in the risk of recurrent deep vein thrombosis (adjusted odds ratio [AOR] 1.74; 95% confidence interval [CI], 1.21–2.51). While history of diabetes was not associated with a significantly increased risk of long-term major bleeding, aspirin therapy at discharge (AOR 1.59; 95% CI, 1.1–2.3) and history of chronic kidney disease (AOR 2.19; 95% CI, 1.44–3.35) were independent predictors of long-term major bleeding after venous thromboembolism diagnosis.

DISCUSSION

Patients with a clinical diagnosis of diabetes who subsequently developed venous thromboembolism were more likely to suffer a complicated clinical course with an increased risk of recurrent deep vein thrombosis and long-term major bleeding. Patients with diabetes had an increased frequency of other clinically important comorbid medical conditions such as immobility, acute infectious illness, heart failure, chronic lung disease, ischemic heart disease, and chronic kidney disease, which increase the risk of venous thromboembolism. Despite a high frequency of comorbidities and risk factors for venous thromboembolism, more than one third of patients with diabetes who were hospitalized for a non-venous-thromboembolism-related condition or had major surgery within the 3 months before diagnosis of deep vein thrombosis or pulmonary embolism did not receive any thromboprophylactic measures. Inferior vena cava filter insertion for treatment of venous thromboembolism was more frequent among patients with diabetes.

Patients with diabetes who subsequently developed venous thromboembolism had a 74% increase in the risk of recurrent deep vein thrombosis following the initial diagnosis, after multivariable adjustment. We hypothesize that the increased rate of immobility and other medical comorbidities, such as heart failure,^{14,15} chronic lung disease,^{16,17} ischemic heart disease,^{1,18} and chronic kidney disease,¹⁹ results in a persistently elevated risk of recurrent venous thromboembolism after treatment of the initial event. However, in multivariable regression analysis including many of these comorbid conditions, only diabetes was a significant independent predictor of recurrent deep vein thrombosis. Discharge from the hospital without a prescription for either low-molecular-weight heparin or warfarin did not account for increased risk of recurrent deep vein thrombosis in diabetic patients. A 2-fold increase in the age-adjusted risk of venous thromboembolism in patients with diabetes identifies the diabetic population as being particularly vulnerable to initial venous thromboembolism and disease recurrence.⁷ Frequent hospitalizations and intensive care unit admissions may contribute to an increased risk of provoked deep vein thrombosis recurrences. High levels of circulating microparticles, a marker for systemic inflammation and a procoagulant state, are present in patients with type 2 diabetes and vascular complications, highlighting an increased risk of thrombosis.²⁰

We also observed a 40% increased risk of long-term major bleeding among patients with diabetes who are diagnosed with venous thromboembolism. Increased medical frailty due to a high frequency of comorbid conditions also may contribute to a higher risk of bleeding associated with antithrombotic therapy. In particular, a higher frequency of chronic kidney disease may predispose to major bleeding in diabetic patients receiving renally cleared antithrombotic medications such as low-molecular-weight heparins. We also observed a higher frequency of aspirin use in patients with diabetes who developed venous thromboembolism. In multivariable regression analysis, both chronic kidney disease and aspirin therapy at discharge were independently associated with long-term major bleeding after venous thromboembolism diagnosis. Diabetes itself may further increase the risk of bleeding. Diabetes is an independent predictor of major bleeding in patients with atherosclerotic cardiovascular disease.^{21,22} Renal function as well as the need for concomitant antiplatelet therapy should be considered when selecting an antithrombotic regimen for diabetic patients who subsequently develop venous thromboembolism.

Although patients with diabetes received venous thromboembolism prophylaxis more frequently than those without diabetes, more than one third did not receive any thromboprophylactic measures. This finding supports previous studies demonstrating underutilization of venous thromboembolism prophylaxis in vulnerable patient populations.^{23–26} Our analysis raises awareness for diabetes as a risk factor for venous

thromboembolism and identifies diabetic patients as a population with a high frequency of comorbid conditions that may contribute to adverse clinical outcomes. Education initiatives for both patients and providers should emphasize venous thromboembolism as a potential complication of diabetes and encourage its prevention.

The present findings should be interpreted in the context of our study design and patient population. The registry population was predominantly white, thereby limiting the ability to generalize our findings. Because a strict definition for diabetes, such as fasting blood glucose ≥ 140 mg/dL or use of insulin or other antidiabetic drugs, was not used, some nondiabetic patients may have been misclassified as diabetics based on a clinical diagnosis. We did not collect data about dose, frequency, or adequacy of thromboprophylaxis or different treatment regimens. As in any observational study, unrecognized confounding may be present despite extensive evaluation of patient characteristics.

To our knowledge, our study represents one of the first registry analyses to evaluate clinical characteristics, thromboprophylactic practices, treatments received, and outcomes in patients with venous thromboembolism and diabetes. The methodology is consistent with published criteria for evaluating the scientific value of clinical data registries.²⁷ Consecutive patients with objectively confirmed venous thromboembolism from urban, suburban, and rural communities were enrolled and comprise a “real world” population.

CONCLUSION

Patients with a clinical diagnosis of diabetes who subsequently developed venous thromboembolism were more likely to suffer a complicated clinical course after venous thromboembolism diagnosis. In particular, diabetes was an independent predictor of recurrent deep vein thrombosis. Despite a high frequency of comorbid conditions contributing to an increased risk of venous thromboembolism, we observed a low rate of thromboprophylaxis in patients with diabetes. Further studies should focus on venous thromboembolism prevention in this vulnerable and increasingly prevalent patient population.

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Appendix

Criteria for Classification of Venous Thromboembolic Events*

Deep vein thrombosis:

Definite: if confirmed by venography, compression ultrasonography, computed tomography, magnetic resonance imaging, or autopsy.

Probable: if the above tests were not performed, or were indeterminate, but impedance plethysmography, radionuclide venography, or radiolabeled fibrinogen scan test results were reported as positive.

Possible: if all of these confirmatory tests were not performed, or were indeterminate, and two of the following three criteria were satisfied: the medical record indicated that the physician made a clinical diagnosis of deep vein thrombosis, symptoms or signs of deep vein thrombosis were documented, or the patient underwent therapy with anticoagulants or inferior vena cava filter insertion.

Pulmonary embolism:

Definite: if confirmed by pulmonary angiography, spiral chest computed tomography, magnetic resonance imaging, or autopsy.

Probable: if the tests above were not performed, or were indeterminate, but ventilation-perfusion lung scan findings were high probability.

Possible: if all of the above confirmatory tests were not performed, or were indeterminate, and two of the following three criteria were satisfied: the medical record indicated that the physician made a clinical diagnosis of pulmonary embolism, symptoms or signs of pulmonary embolism were documented, or the patient underwent therapy with anticoagulants or inferior vena cava filter insertion.

*Modified from criteria previously utilized by Silverstein et al in the Olmstead County study of venous thromboembolism.¹² Given increasing acceptance over the last decade of compression ultrasonography as a single diagnostic modality for deep vein thrombosis, we have classified patients with deep vein thrombosis confirmed by compression ultrasonography as definite, whereas these patients would have been categorized as probable by Silverstein's criteria.

CLINICAL SIGNIFICANCE

- Diabetic patients who developed venous thromboembolism had an increased risk of recurrent deep vein thrombosis and long-term major bleeding.
- Diabetes was an independent risk factor for recurrent deep vein thrombosis.
- More than one third of diabetic patients who were hospitalized for a non-venous-thromboembolism-related condition or had major surgery within the 3 months before venous thromboembolism diagnosis did not receive thromboprophylaxis.

Table 1

Baseline Characteristics of Patients with Venous Thromboembolism According to History of Diabetes

	Diabetes (n = 476)	No Diabetes (n = 2012)	P Value
Age, years (mean $\pm$ SD)	68.2 $\pm$ 14.4)	62.8 $\pm$ 18.8	<.001
Age >65 years, n (%)	309 (64.9)	1023 (50.8)	<.001
Body mass index, kg/m ² (mean $\pm$ SD)	31.0 $\pm$ 9.2	28.1 $\pm$ 7.1	<.001
Male, n (%)	217 (45.6)	887 (44.1)	.58
Female, n (%)	259 (54.4)	1120 (55.7)	.58
Ethnicity, n (%)			
Caucasian	425 (89.3)	1806 (89.8)	.76
African-American	23 (4.8)	58 (2.9)	.04
Asian	1 (0.2)	10 (0.5)	.35
Hispanic	13 (2.7)	30 (1.5)	.08
Other	4 (0.8)	17 (0.8)	.99
Unknown	10 (2.1)	91 (4.5)	.01
Developed venous thromboembolism during hospitalization for another condition, n (%)	182 (38.2)	518 (25.8)	<.001
Length of stay, days (mean $\pm$ SD)	13.8 $\pm$ 22.0	9.7 $\pm$ 14.1	.001

Table 2

Comorbid Conditions in Patients with Venous Thromboembolism According to History of Diabetes

	Diabetes (n = 476)	No Diabetes (n = 2012)	P Value
Hypertension, n (%)	378 (79.4)	970 (48.2)	<.001
Immobility > 48 hours, n (%)	250 (52.5)	877 (43.6)	<.001
Smoking history, * n (%)			
Current smoker	53 (15.1)	292 (19.9)	.03
Former smoker	144 (40.9)	456 (31.0)	.001
Never smoker	147 (41.8)	607 (41.3)	.87
Dyslipidemia, n (%)	190 (39.9)	495 (24.6)	<.001
Acute infectious illness, n (%)	163 (34.2)	463 (23.0)	<.001
Heart failure, n (%)	146 (30.7)	285 (14.2)	<.001
Indwelling central venous catheter, n (%)	137 (28.8)	323 (16.1)	<.001
Major surgery within the previous 3 months, n (%)	135 (28.4)	550 (27.3)	.65
Active cancer or history of cancer, n (%)	130 (27.3)	524 (26.0)	.57
Intensive care unit discharge within the previous 3 months, n (%)	122 (25.6)	284 (14.1)	<.001
Chronic obstructive pulmonary disease, n (%)	120 (25.2)	364 (18.1)	.001
Ischemic heart disease, n (%)	116 (24.4)	208 (10.3)	<.001
ST-elevation myocardial infarction	9 (1.9)	14 (0.7)	.03
Non-ST-elevation myocardial infarction	14 (2.9)	36 (1.8)	.13
Unspecified myocardial infarction	70 (14.7)	156 (7.8)	<.001
Any myocardial infarction	89 (18.7)	199 (9.9)	<.001
Unstable angina *	27 (7.7)	50 (3.4)	.001
Stable angina *	48 (13.6)	70 (4.8)	<.001
Prior venous thromboembolism, n (%)	79 (16.6)	371 (18.4)	.34
Cardiac procedure during admission, n (%)	78 (16.4)	171 (8.5)	<.001
Catheterization or EP study	59 (12.4)	121 (6.0)	<.001
PCI and stent	25 (5.3)	48 (2.4)	.002
Pacemaker	22 (4.6)	44 (2.2)	.01
ICD implantation	11 (2.3)	10 (0.5)	.001
Cerebrovascular disease, n (%)	75 (15.8)	208 (10.3)	.001
Peripheral artery disease, n (%)	73 (15.3)	109 (5.4)	<.001
Chronic kidney disease, n (%)	73 (15.3)	123 (6.1)	<.001
Dialysis dependent	27 (5.7)	36 (1.8)	<.001
Prior positive cardiac catheterization or PCI, * n (%)	46 (13.1)	62 (4.2)	<.001
Prior coronary artery bypass surgery, * n (%)	41 (11.7)	64 (4.4)	<.001

EP = electrophysiology; ICD = implantable cardiac defibrillator; PCI = percutaneous coronary intervention.

* Data not collected on this variable in 2005 (patients with diabetes, n = 352; patients without diabetes, n = 1470).

Table 3**Clinical Presentation of Venous Thromboembolism According to History of Diabetes**

	Diabetes (n = 476)	No Diabetes (n = 2012)	P Value
Any symptoms of venous thromboembolism, n (%)	365 (76.7)	1624 (80.7)	.05
Extremity swelling, n (%)	217 (45.6)	946 (47.0)	.57
Extremity pain, n (%)	114 (24.0)	642 (31.9)	.001
Dyspnea, n (%)	106 (22.3)	457 (22.7)	.83
Tachycardia (heart rate >100 beats per minute), n (%)	57 (12.0)	199 (9.9)	.17
Cough, n (%)	38 (8.0)	153 (7.6)	.78
Chest pain, n (%)	37 (7.8)	213 (10.6)	.06
Hypotension (systolic blood pressure <100 mm Hg), n (%)	33 (6.9)	120 (6.0)	.41
Fever, n (%)	31 (6.5)	125 (6.2)	.81
Hypoxemia (oxygen saturation <90%), n (%)	12 (2.5)	43 (2.1)	.90
Loss of consciousness, n (%)	12 (2.5)	24 (1.2)	.04
Any deep vein thrombosis, n (%)	422 (88.7)	1710 (85.0)	.03
Unprovoked (idiopathic) venous thromboembolism, n (%)	79 (16.6)	547 (27.2)	<.001
Proximal lower-extremity with calf deep vein thrombosis, n (%)	66 (13.9)	243 (12.1)	.29
Proximal lower-extremity without calf deep vein thrombosis, n (%)	202 (42.4)	848 (42.2)	.91
Pulmonary embolism, n (%)	131 (27.5)	573 (28.5)	.69
Pulmonary embolism and deep vein thrombosis, n (%)	79 (16.6)	271 (13.5)	.08
Upper-extremity deep vein thrombosis, n (%)	75 (15.8)	219 (10.9)	.004
Isolated calf deep vein thrombosis, n (%)	33 (6.9)	160 (8.0)	.45

Table 4

Characteristics of Prophylaxis in Patients with Hospitalization or Major Surgery Within 3 Months of Subsequently Developing Venous Thromboembolism According to History of Diabetes *

	Diabetes (n = 476)	No Diabetes (n = 2012)	P Value
Receiving any prophylaxis, n (%)	253 (60.4)	774 (46.6)	<.001
Pneumatic compression devices, n (%)	134 (32.0)	430 (25.9)	.01
Subcutaneous unfractionated heparin, n (%)	129 (30.8)	325 (19.6)	<.001
Low-molecular-weight heparin, n (%)	47 (11.2)	141 (8.5)	.09
Intravenous unfractionated heparin, n (%)	41 (9.8)	87 (5.2)	.001
Warfarin, n (%)	24 (5.7)	75 (4.5)	.31

* Patients could have received >1 prophylactic modality.

Table 5

Therapy in Patients with Venous Thromboembolism According to History of Diabetes *

	Diabetes (n = 476)	No Diabetes (n = 2012)	P Value
Initial therapy			
Warfarin, n (%)	306 (64.3)	1285 (63.9)	.86
Intravenous unfractionated heparin, n (%)	238 (50.0)	941 (46.8)	.20
Low-molecular-weight heparin, n (%)	222 (46.6)	1040 (51.7)	.05
Inferior vena cava filter, n (%)	74 (15.6)	220 (10.9)	.01
Subcutaneous unfractionated heparin, n (%)	28 (5.9)	66 (3.3)	.01
Fibrinolysis for venous thromboembolism, n (%)	12 (2.5)	28 (1.4)	.10
Other parenteral anticoagulant, n (%)	11 (2.3)	31 (1.5)	.26
Discharge therapy			
Warfarin alone, n (%)	182 (40.8)	752 (39.0)	.48
Low-molecular-weight heparin alone, n (%)	33 (7.4)	173 (9.0)	.28
Low-molecular-weight heparin and warfarin, n (%)	122 (27.4)	650 (33.7)	.01
Neither, n (%)	109 (24.4)	354 (18.4)	.004

* Patients could have received >1 therapeutic modality.

Table 6

Outcomes of Patients with Venous Thromboembolism According to History of Diabetes

	Diabetes (n = 476)	No Diabetes (n = 2012)	P Value
No complications, n (%)	309 (64.9)	1457 (72.4)	.001
Recurrent pulmonary embolism, * n (%)	8 (1.7)	30 (1.5)	.76
Recurrent deep vein thrombosis, * n (%)	71 (14.9)	216 (10.7)	.01
Long-term major bleeding, * n (%)	78 (16.4)	235 (11.7)	.01
In-hospital major bleeding, n (%)	27 (5.7)	76 (3.8)	.07
Heparin-induced thrombocytopenia, * n (%)	6 (1.3)	19 (0.9)	.70
In-hospital death, n (%)	30 (6.3)	83 (4.1)	.05
Death within 30 days of venous thromboembolism diagnosis, n (%)	45 (9.9)	146 (7.5)	.10

* Long-term outcomes data encompassed a median follow-up period of 992 days.