Venous Thromboembolism in the Outpatient Setting

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Background: There has been great interest in optimizing prophylaxis against venous thromboembolism (VTE) in the hospital setting. However, data from earlier studies suggest that most VTEs occur in the outpatient setting. The purposes of this observational study were to describe the frequency of VTEs occurring in the outpatient setting, characterize the prevalence of previously identified risk factors for VTE, and identify previous use of VTE prophylaxis.

Methods: The medical records of residents from the Worcester metropolitan area diagnosed as having *International Classification of Diseases, Ninth Revision* codes consistent with possible VTE during 1999, 2001, and 2003 were independently validated and reviewed by trained abstractors.

Results: A total of 1897 subjects had a confirmed episode of VTE. In all, 73.7% of patients developed VTE in the outpatient setting; a substantial proportion of these patients had undergone surgery (23.1%) or hospitalization (36.8%) in the preceding 3 months. Among these patients, 67.0% experienced VTE within 1 month of the preceding hospital encounter. Other major risk factors for VTE in the outpatient setting included active malignant neoplasm (29.0%) or previous VTE (19.9%). Among 516 patients with a recent hospitalization who subsequently developed VTE, less than half (42.8%) had received anticoagulant prophylaxis for VTE during that visit.

Conclusions: More VTEs were diagnosed in the 3 months following hospitalization than during hospitalization. Efforts to improve in-hospital use of VTE prophylaxis may help decrease the incidence of outpatient VTE. However, given the shortening of hospital stays, studies of extended VTE prophylaxis following hospital discharge are warranted.

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DATA FROM THE POPULATION-based Worcester DVT (deep vein thrombosis) Study in the mid to late 1980s suggested that most episodes of venous thromboembolism (VTE) take place in the outpatient setting.[1] Nevertheless, data from another population-based study (Olmsted County, Minnesota) suggest that factors associated with hospitalization accounted for nearly 50% of the attributable risk of VTE.[2]

See also pages 1451 and 1476

The risk factor profile of outpatients experiencing VTE, particularly with respect to recent hospitalizations and surgical procedures, has not been well described. The objectives of this observational study were to identify the proportion of patients with VTE in a community who experience their events in the outpatient setting, to characterize the prevalence of previously identified risk factors for VTE, and to identify previous use (or nonuse) of VTE prophylaxis.

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METHODS

Computerized printouts of all Worcester residents with health care system encounters in which any of 34 *International Classification of Diseases, Ninth Revision (ICD-9)* diagnosis codes possibly consistent with the occurrence of VTE had been listed in 1999, 2001, and 2003 were obtained from each of 12 hospitals serving residents of the Worcester standard metropolitan statistical area. These data queries were not limited to discharge diagnoses but also encompassed all outpatient, emergency department, radiology department, and laboratory encounters. For the first study cohort, the logs and/or computerized billing lists of patients evaluated in area radiology departments for potential DVT were also screened. This was done to identify potential cases of VTE in greater Worcester residents that may have been missed owing to coding errors and to identify patients referred directly from outside physicians' offices, rehabilitation facilities, and nursing homes for testing who then returned directly to these outside settings for treatment. Because this additional screen identified only a few additional cases of VTE, and in only 1 of 11 hospitals, this screening process was not performed in the other 10 hospitals in 2001 and 2003.

The medical records of all identified patients meeting the geographic inclusion criteria (residents of the Worcester standard metropolitan statistical area; 2000 census population, 477 800) were reviewed. Trained abstractors using prespecified criteria validated and characterized each case of VTE as definite, probable, possible, or absent. These criteria were based on a modification of a classification schema proposed by Silverstein et al.[3] Each case and its classification were also validated by the study project coordinator (C.E.). If the classification of VTE was not immediately clear when using the criteria specified, the medical record was reviewed by the principal investigator (F.A.S.). Incident cases of VTE were defined as those occurring in patients without any history of upper or lower extremity DVT or pulmonary embolism (PE). Potential cases of recurrent VTE were classified using criteria similar to those used for incident cases; however, the development of a definite or probable recurrence of VTE required the new occurrence of thrombosis in a previously uninvolved venous or pulmonary segment.

The medical records of each patient's current and previous hospitalizations and/or outpatient visits were reviewed to identify whether the index VTE represented an incident (initial) or a recurrent case. Ambulatory patients presenting to the hospital with signs and symptoms consistent with VTE, or diagnosed as having VTE within 24 hours of hospital presentation, were considered to have developed VTE in the outpatient setting.

DATA COLLECTION

Information was collected about patients' demographic characteristics, medical history, clinical characteristics, and diagnostic test results and hospital management practices. Only medical history variables documented in patients' medical records by a physician were abstracted. For variables in which a number of medical record entries were possible, data abstractors were instructed to record only entries matching those on a prespecified list. For example, cardiac procedures were defined to include only electrophysiology studies, percutaneous coronary interventions, pacemaker implantation, and implantable cardiac defibrillator placement. For purposes of analysis, infections were limited to those involving the blood (laboratory-confirmed clinical bacteremia or sepsis), bones and joints, central nervous system, cardiovascular system, gastrointestinal tract system, respiratory system (pneumonia only), surgical sites, or the skin. Only infections considered serious enough to be documented in the medical record were included. The variable *surgery* included major operations during which general or epidural anesthesia lasted 30 minutes or longer. Medical history variables defined as "recent" were those occurring or active in the 3 months preceding the diagnosis of VTE.

Although information about recent hospitalizations and/or surgical procedures was usually available in the index medical record, previous medical records were also searched for hospitalizations and/or surgical procedures occurring in the 3 months preceding the index VTE diagnosis. A focus of our data abstraction efforts was to identify the proportion of patients experiencing VTE in the outpatient setting who recently had been hospitalized or had undergone surgery and the timing of previous hospitalizations and surgical procedures relative to the VTE. From the index and previous medical records, use of VTE prophylaxis during previous hospitalizations (at any time until discharge) or following surgery (at any time until hospital discharge) was also recorded.

DATA ANALYSIS

Differences in the distribution of various demographic and clinical characteristics between patients who presented with VTE from the outpatient setting, compared with those who were diagnosed as having VTE during hospitalization, were examined using χ^2 tests of statistical significance for categorical variables and 2-tailed *t* tests for continuous variables. On the basis of prevalence, as well as clinical importance, we described the proportion of outpatients who had 0, any 1, any 2 or 3, or any 4 or all 5 of the following VTE risk factors: recent hospitalization, recent surgery, active malignant neoplasm, recent infection, or previously documented episode of VTE. To better understand the temporal relationship between previous hospital encounters and development of subsequent VTE, we stratified outpatients with VTE following hospitalization or surgery into 1 of 3 groups: onset of VTE within 1 month (≤29 days) of a hospital encounter, onset of VTE from 1 to 2 months (30-59 days) after an encounter, and onset of VTE from 2 to 3 months (60-90 days) after a recent hospitalization or surgical procedure.

Because we were particularly interested in examining missed opportunities for prevention in outpatients who developed VTE, we also described the use of VTE prophylaxis during previous hospitalization in the subset of outpatients with VTE who had been hospitalized in the preceding 3 months. This was carried out in the overall study sample and in patients further stratified according to the presence of several predefined major risk factors for VTE (recent surgery, active malignant neoplasm, recent infection, and previous VTE).

RESULTS

A total of 7222 medical records were identified using predefined *ICD-9* codes in which cases of VTE might have been diagnosed (2333 for 1999, 2462 for 2001, and 2427 for 2003). All of these records were reviewed for validation of VTE. A total of 1897 Worcester residents experienced an independently validated episode of DVT (n=1348), PE (n=285), or both (n=264) during the 3 study years. Approximately 96.3% of cases of DVT were classified as definite, 0.2% as probable, and 3.5% as possible. Of the 285 validated cases of PE, 50.0% were classified as definite, 22.7% as probable, and 27.3% as possible. All remaining cases of potential VTE were classified as negative for acute VTE after medical record review.

Of these 1897 validated cases of VTE, 1399 (73.7%) presented from the outpatient setting with signs and symptoms consistent with VTE and/or had VTE diagnosed within 1 day of hospital admission.

MEDICAL CHARACTERISTICS OF OUTPATIENTS WITH VTE

A large proportion of patients presenting with VTE from the outpatient setting had recently been hospitalized (36.8%) or had undergone major surgery (23.1%) during the preceding 3 months. In all, 29.0% had a recent or active diagnosis of malignant neoplasm, 18.6% had experienced a recent infection, and 19.9% had previously had a VTE (**Table 1**). Among outpatients with VTE, 29.5% had none, 31.8% had only 1, 34.1% had any 2 or 3, and 2.7% had any 4 or all 5 of the previously described risk factors for VTE. For comparative purposes, the prevalence of these characteristics in patients who developed and were diagnosed as having VTE during hos-

Table 1. Demographic and Clinical Characteristics of Patients According to Setting of VTE (Outpatient vs Inpatient)[a]

Characteristic	Outpatient (n = 1399)	Inpatient (n = 498)	*P* Value
Demographic Factors			
Age, mean, y	63.3	67.4	<.001
Age, y			
<55	33.0	21.2	<.001
55-64	13.9	17.2	
65-74	18.7	18.8	
≥75	34.5	42.8	
Female	56.2	51.9	.09
BMI[b]			
<25.0	31.5	37.9	.11
25.0-29.9	32.4	29.6	
≥30.0	36.1	32.5	
Medical History			
Recent prior hospitalization (without surgery)[c]	18.9	23.7	<.001
Recent surgery (without hospitalization)[c]	5.2	19.1	<.001
Recent prior hospitalization and surgery[c]	17.9	20.9	<.001
Recent malignant neoplasm[c]	29.0	32.3	.17
Recent infection[c]	18.6	46.8	<.001
Recent central venous catheter[c]	10.4	41.0	<.001
Previous DVT	17.4	8.6	.001
Previous PE	6.0	2.9	<.05
Previous DVT or PE	19.9	10.2	<.001
Recent intensive care unit discharge[c]	8.7	38.2	<.001
Recent hormonal therapy[c]	8.0	3.0	<.001
Recent fracture[c]	7.3	18.7	<.001
Recent chemotherapy[c]	7.7	8.0	.82
Recent heart failure[c]	4.2	16.5	<.001
Recent cardiac procedures[c]	2.9	7.8	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

[a] Data are given as percentage of patients, unless otherwise indicated. Because of rounding, percentages for demographic factors may not total 100. In addition, some patients had more than 1 risk factor in their medical history.

[b] In all, 639 of the patients (33.7%) were missing data for BMI.

[c] *Recent* indicates active or occurring within 3 months of diagnosis of VTE.

pitalization is also provided in Table 1. Patients who developed VTE in the outpatient setting tended to be younger; were less likely to have been previously hospitalized, to have been admitted to an intensive care unit, to have had a central venous catheter placed, or to have undergone surgery; and were less likely to have had a recent fracture, heart failure, or infection than patients who developed VTE in the inpatient setting. These patients were also more likely to have a history of DVT or PE or to have been taking hormonal therapy.

TIMING OF VTE RELATIVE TO PRECEDING HOSPITALIZATION OR SURGERY

Of VTE episodes occurring within 3 months of a prior hospitalization, 67.0% occurred within the first month following hospital discharge. The median and mean lengths of the preceding hospital stay for patients developing VTE within 3 months of the present hospitalization were 4.0 and 7.4 days, respectively.

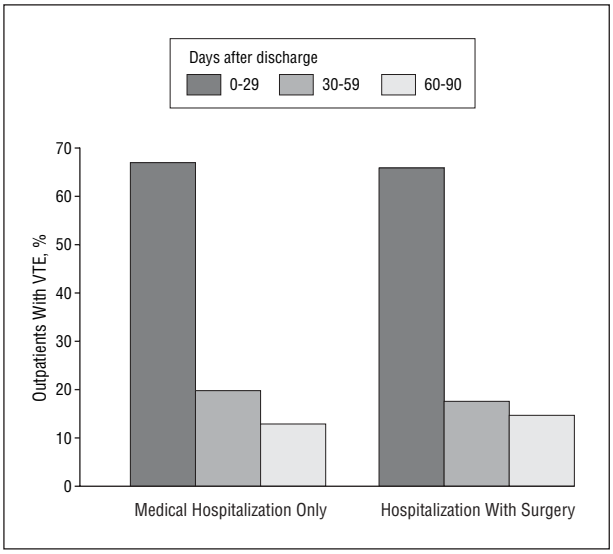

Figure. Timing of diagnosis of venous thromboembolism (VTE) relative to the preceding hospital discharge among individuals who developed VTE as an outpatient.

Among patients who had recently been hospitalized but had not undergone surgery, 66.9% were diagnosed as having VTE within 1 month after hospital discharge, 19.9% between 1 and 2 months after hospital discharge, and the remainder (13.2%) between 2 and 3 months from the time of hospital discharge. Among patients who had been hospitalized, and had undergone recent surgery, 66.4% had been diagnosed as having VTE within 1 month after surgery, 18.3% from 1 to 2 months after hospital discharge, and 15.2% from 2 to 3 months after hospital discharge (**Figure**).

HISTORY OF VTE PROPHYLAXIS

We examined the use of prophylaxis for VTE during the preceding hospitalization overall and for different categories of outpatients with VTE who had been hospitalized in the preceding 3 months: (1) those with none of the other major risk factors for VTE (recent surgery, active malignant neoplasm, recent infection, and previous VTE); (2) those with recent surgery; (3) those with active malignant neoplasm; (4) those with previous VTE; (5) those with recent infection; and (6) those with any 2 or 3 or more of these major risk factors (**Table 2**). Approximately 3 of 5 previously hospitalized patients (59.7%) received any form of VTE prophylaxis during their hospitalization: 42.8% received anticoagulant prophylaxis (with or without mechanical prophylaxis) and an additional 16.9% received only mechanical prophylaxis. Similar utilization patterns of therapies for the prevention of VTE were seen in each of our prespecified patient subsets with the exception of patients with a history of previous VTE or 3 or more risk factors, in which slightly higher rates of VTE prophylaxis were observed.

Table 2. Use of Prophylaxis for Venous Thromboembolism (VTE) During Preceding Hospitalization in Outpatients With VTE According to Existing Risk Factors

Patient Group, Risk Factor	Any VTE Prophylaxis, %	Anticoagulant Prophylaxis With or Without Mechanical Prophylaxis, %	Mechanical Prophylaxis Only, %
All previously hospitalized patients (n = 516)	59.7	42.8	16.9
Patient subset			
Previous VTE (n = 73)	74.0	53.4	20.6
Recent surgery (n = 251)	61.6	46.2	15.4
Active malignant neoplasm (n = 185)	63.8	42.7	21.1
Recent infection (n = 170)	60.0	44.1	15.9
None of the above (n = 84)	54.8	40.5	14.3
Any 2 of the above (n = 168)	64.9	47.0	17.9
≥3 of the above (n = 37)	73.0	56.8	16.2

COMMENT

Almost 2 decades ago, findings from the initial Worcester DVT study suggested that VTE was an "outpatient disease."[1] In our contemporary population-based study of greater Worcester residents, this remains the case—the vast majority (73.7%) of patients diagnosed as having VTE presented from the outpatient setting. Nevertheless, almost half of these patients had been hospitalized or undergone surgery in the preceding 3 months. While reducing the risk of VTE in hospitalized patients is important, our findings suggest that decreasing the occurrence of VTE after hospital discharge may have even more of an influence on the overall VTE burden. Although we cannot assess the magnitude of VTE risk associated with specific surgery types, hospital diagnoses, or comorbidities, we described the profile of outpatients experiencing VTE in the community, characterized the temporal relationship between VTE and previous hospital encounters, and determined whether VTE prophylaxis was provided during those encounters.

Of outpatients presenting with VTE, 36.8% had been hospitalized in the preceding 3 months—half of these for medical reasons only and half to undergo surgery during the hospitalization. These data are consistent with the findings from the Olmsted County study in which the attributable risk associated with VTE for a number of different risk factors was examined.[2] In that study of greater Rochester, Minnesota, residents, factors associated with hospitalization were estimated to have accounted for nearly half (46%) of all cases of VTE occurring in the community setting. As in the results of our study, hospitalization for surgery and for medical illness accounted for a similar proportion of independently validated cases of VTE.

The use of VTE prophylaxis during a previous hospitalization in patients with subsequent VTE in the outpatient setting was far from optimal. Only 59.7% of patients had received any form of prophylaxis and only 42.8% had received anticoagulant prophylaxis during their preceding hospital stay. Because most of the cases of VTE occurred within 29 days of hospital discharge (and 41.0% occurred within 14 days), it is not unreasonable to assume that some of these cases may have been prevented simply by increased use of appropriate in-hospital DVT prophylaxis (eg, compression stockings, pneumatic compression devices, and, in high-risk patients, anticoagulants). Approximately half of the outpatients who experienced VTE following hospitalization had a length of stay that was 4 days or less. These data suggest that omission of VTE prophylaxis in patients with anticipated short hospital stays may not be appropriate. It is also important to recognize that, because of decreasing lengths of hospital stays, the duration of in-hospital DVT prophylaxis has been shortened and there may be increased periods of immobilization among outpatients. During the study period (1999-2003), prescription of DVT prophylaxis following hospital discharge was not an accepted practice (except in a small proportion of patients undergoing hip or knee surgery). One could speculate that even more cases of VTE may be prevented by the judicious application of DVT prophylaxis following hospital discharge. Previous studies[4-8] have documented that symptomatic VTE often occurs after discharge from the hospital in patients who have undergone orthopedic surgery, that "silent" thrombus present early after surgery can extend after DVT prophylaxis is discontinued, and that prophylaxis following hospital discharge in these patients is efficacious and cost-effective. Studies evaluating the efficacy—as well as the cost-effectiveness—of outpatient DVT prophylaxis following hospital discharge in other high-risk populations (including those with serious medical conditions) are needed.

Finally, patients with a malignant neoplasm constituted approximately one-third of all cases of outpatient VTE in our study. Previous studies[9] have suggested that patients with cancer have up to a 6-fold increased risk of VTE compared with those without cancer. Among patients undergoing similar surgical procedures, those with an active malignant neoplasm have a 2- to 3-fold increased risk of VTE compared with those without cancer.[10-12] Patients with cancer are also more likely to experience VTE after surgery, despite provision of VTE prophylaxis.[13,14] Given the extraordinarily high risk of VTE in patients with cancer, the American College of Chest Physicians guidelines strongly recommend (grade 1A) VTE prophylaxis in these patients when they undergo surgery or are hospitalized.[15] In our study sample, patients with a malignant neoplasm who developed VTE as an outpatient received suboptimal DVT prophylaxis during previous recent hospitalizations or surgical procedures.

Approximately half of the patients with a malignant neoplasm and outpatient VTE had neither a recent hospitalization nor a previous surgical procedure. Unfortunately, data on the utility and/or cost-effectiveness of DVT prophylaxis in patients with cancer but no other indication are limited. Study of this population has been difficult because of the heterogeneity of cancer types and treatments. Although the use of low-dose warfarin or low-molecular-weight heparin therapy has been associated with a decreased incidence of VTE in some earlier studies[16,17] of patients with advanced cancer or those receiving chemotherapy, other studies[18,19] have not been able to dem-

onstrate a benefit from long-term DVT prophylaxis in patients with cancer and indwelling central venous catheters.[16-19] Accordingly, the American College of Chest Physicians guidelines recommend against the use of anticoagulant prophylaxis in patients with cancer but without a traditional indication for DVT prophylaxis.[15] Because those patients made up a sizable proportion of all patients experiencing VTEs in the greater Worcester community, further study of DVT prophylaxis in ambulatory patients with cancer is clearly needed.

As in the design and conduct of any observational study, the present investigation has several limitations. Although we conducted a broad screening for possible cases of VTE that may have occurred in greater Worcester residents by using multiple databases, validated each potential case of VTE, and performed regular audits of randomly selected charts, it is likely that we may have missed some cases of VTE—in particular, cases of VTE occurring in Worcester residents who sought care at outside hospitals and cases of PE resulting in out-of-hospital death. Another potential limitation is that, while our data abstracters were provided with prespecified definitions of medical history variables of interest, they still had to rely on documentation of those conditions in the medical record. As such, the possibility of overestimation or underestimation of the prevalence of specific risk factors for VTE cannot be excluded.

Because we collected data on only the most recent hospitalization or surgical procedure that may have occurred in the 3 months preceding VTE, we cannot comment on the proportion or characteristics of patients with VTE who had multiple hospitalizations during that period. Finally, because the Worcester VTE study does not capture data on a control population of outpatients without VTE, we cannot directly assess the magnitude of VTE risk associated with previous hospitalizations, surgery types, or malignant neoplasms. Similarly, we cannot comment on the effect of use or nonuse of DVT prophylaxis during high-risk scenarios.

In conclusion, our study provides insight into the profile of patients who experience outpatient VTE within this well-defined, large, and representative northeastern community. These patients ultimately represent a significant proportion of our failures in VTE prevention. The results of our descriptive epidemiologic investigation provide insight into the characteristics of potentially high-risk patient subsets who may benefit from the use of outpatient prophylaxis for prevention of VTE. Further characterization of this high-risk patient profile in additional observational studies will generate testable hypotheses and subsequent investigations that will ultimately reduce the number of these failures.

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