A Prospective Registry of 5,451 Patients With Ultrasound-Confirmed Deep Vein Thrombosis

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We enrolled 5,451 patients with ultrasound-confirmed deep vein thrombosis (DVT), including 2,892 women and 2,559 men, from 183 United States sites in our prospective registry. The 5 most frequent co-morbidities were hypertension (50%), surgery within 3 months (38%), immobility within 30 days (34%), cancer (32%), and obesity (27%). Of the 2,726 patients who had their DVT diagnosed while in the hospital, only 1,147 (42%) received prophylaxis within 30 days before diagnosis.

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Venous thromboembolism (VTE) comprises deep vein thrombosis (DVT) and pulmonary embolism (PE) and accounts for >250,000 hospitalizations annually in the United States.[1,2] The most serious complication of DVT is PE, which has a 3-month mortality rate as high as 17%.[3–5] VTE can also lead to the debilitating postphlebitic syndrome in as many as 1/3 of patients.[6] The incidence of DVT varies with the population studied, ranging from 56 cases/100,000 to 182 cases/100,000 patients.[1,7] Particularly susceptible groups include elderly hospitalized patients and patients who have had recent surgery, cancer, or previous DVT.[2,8–10] To explore the current epidemiology of patients with DVT, as well as the current management and use of prophylaxis, we undertook a large, prospective multicenter registry of United States patients whose acute DVT was diagnosed using venous ultrasonography. We describe the demographics, co-morbidities, clinical presentation, prophylaxis, and initial treatment of these patients.

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We enrolled consecutive patients with acute DVT confirmed by venous ultrasound at 183 United States sites in a multicenter prospective study. The maximum enrollment period was 6 months (October 2001 to March 2002). There were no exclusion criteria. We classified patients as outpatients (including those seen in the emergency department) or inpatients based on their status at the time of DVT diagnosis.

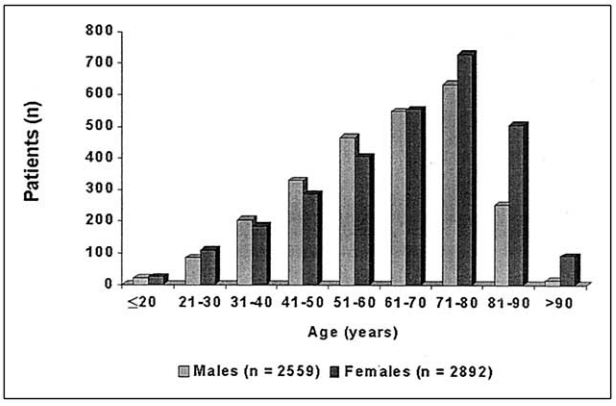

FIGURE 1. Distribution of patients by age and gender.

Investigational review board approval was obtained as was patient consent, if required. Data on consecutive patients who had DVT diagnosed using ultrasound were obtained from medical records at each study site and recorded on case record forms by a study coordinator. Co-morbidities were prespecified in our protocol. Each site with >2 patients was monitored with at least 1 site visit by an independent auditor to confirm the ultrasound diagnosis and to review the medical records to ensure accuracy. Statistical Analysis System version 6.12 (SAS Insitute, Cary, North Carolina) was used to calculate statistics.

We enrolled 5,451 patients (2,892 women; 2,559 men), of whom 2,725 were outpatients and 2,726 were inpatients; 1,364 patients were surgical and 1,362 were nonsurgical. The diagnosis of DVT among inpatients was obtained after a median of 6 hospital days among surgical patients versus 2 hospital days among nonsurgical patients ($p < 0.001$). Figure 1 shows the age distribution for men and women. The mean age was 64 ± 17 years. There were more women than men ≥70 years of age ($p < 0.0001$). In addition, 72% of patients were white (n = 3,928), 17% were African-American (n = 930), 4% were Hispanic (n = 210), <1% were Asian (n = 23), 1% represented other races (n = 41), and 6% were missing information on race (n = 319). Concomitant PE was identified in 14.5% of patients (n = 793). PE was confirmed by >1 modality in some patients: lung scan (n = 402), chest computed axial tomography (n = 402), contrast pulmonary angiography (n = 48), and magnetic resonance imaging (n = 2).

Of the patients, 876 (16%) had no co-morbidities. The most frequent co-morbidities were hypertension, surgery within 3 months before diagnosis, immobility

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*The members of the DVT FREE Steering Committee are listed in the Appendix.

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TABLE 1 Co-morbid Conditions by Status at Time of Deep Vein Thrombosis (DVT) Diagnosis in Descending Order of Frequency

Conditions	All (n = 5,451)	Patient Status at Time of Diagnosis: Outpatient (n = 2,725)	Patient Status at Time of Diagnosis: Inpatient (n = 2,726)
Systemic hypertension	2,707 (50%)	1,206 (45%)	1,501 (55%)
Surgery past 3 mos	2,094 (38%)	732 (35%)	1,362 (65%)
Immobile last 30 d	1,876 (34%)	537 (29%)	1,339 (71%)
Cancer	1,768 (32%)	836 (47%)	932 (53%)
Obesity	1,466 (27%)*	709 (48%)	757 (52%)
Previous smoker	1,424 (26%)	636 (45%)	788 (55%)
Previous hospitalization	1,255 (23%)	524 (42%)	731 (58%)
Previous DVT	1,220 (22%)	692 (57%)	528 (43%)
Neurologic disease	1,183 (22%)	484 (41%)	699 (59%)
Osteoarthritis	878 (16%)	430 (49%)	448 (51%)
In-dwelling catheter	840 (15%)	196 (23%)	644 (77%)
Current smoker	758 (14%)	418 (55%)	340 (45%)
Non–insulin-dependent diabetes mellitus	689 (13%)	327 (47%)	362 (53%)
Congestive heart failure	685 (13%)	225 (33%)	460 (67%)
Chronic obstructive pulmonary disease	668 (12%)	254 (38%)	414 (62%)
Other infectious disease	566 (10%)	180 (32%)	386 (68%)
Insulin-dependent diabetes mellitus	418 (8%)	119 (28%)	299 (72%)
Hormone replacement therapy	404 (7%)†	262 (65%)	142 (35%)
Pneumonia	401 (7%)	78 (19%)	323 (81%)
Previous pulmonary embolism	364 (7%)	204 (56%)	160 (44%)
Fracture	289 (5%)	87 (30%)	202 (70%)
Thrombophilic disorder	254 (5%)	141 (56%)	113 (44%)
Sepsis	252 (5%)	25 (10%)	227 (90%)
Family history of VTE	244 (4%)	168 (69%)	76 (31%)
Minor trauma	200 (4%)	116 (58%)	84 (42%)
Chronic venous insufficiency	199 (4%)	96 (48%)	103 (52%)

*BMI $\geq$30 kg/m^2; 33% of patients with known height and weight.
†Fourteen percent of women.

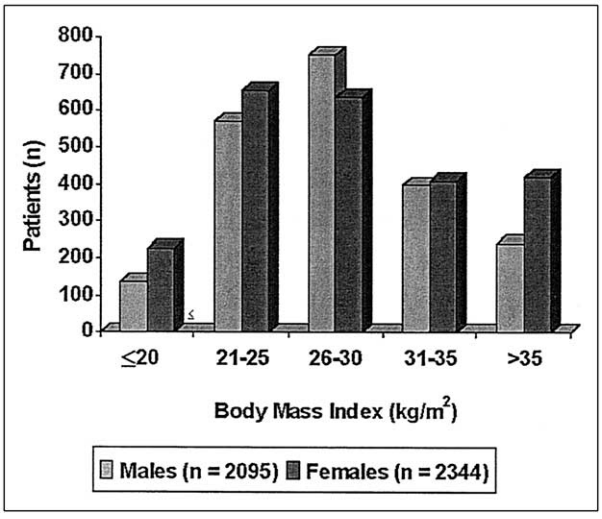

FIGURE 2. Distribution of patients by BMI and gender. BMI data are missing for 744 patients.

within 30 days before diagnosis, cancer, and obesity (Table 1). Overweight and obesity were common (Figure 2). Body mass index (BMI) was calculated for 81% of all patients (n = 4,439). The mean BMI was 28.3 $\pm$ 7.3 kg/m^2. One third of patients were obese (BMI >30 kg/m^2), and 31% were overweight (BMI 25 kg/m^2 to 30 kg/m^2). A total of 2,094 (38%) developed DVT within 3 months after surgery (Figure 3). The median time from surgery to diagnosis of DVT was 8 days for patients who had their DVT diagnosed while in hospital and 21 days for those who had their DVT diagnosed while outpatients ($p < 0.0001$).

Among the 793 patients with concomitant PE, the co-morbidities more commonly observed than with DVT alone were chronic lung disease (16% vs 12%, p = 0.004) and pulmonary infection (10% vs 8%, p = 0.04). Less commonly observed co-morbidities among patients with concomitant PE and DVT were insulin-dependent diabetes mellitus (5% vs 8%, p = 0.007), kidney disease requiring hemodialysis (1% vs 4%, $p < 0.001$), infectious diseases other than pulmonary infection (7% vs 10%, p = 0.004), and gastrointestinal bleeding requiring transfusion (1% vs 3%, p = 0.007).

Most patients (90%; n = 4,907) experienced clinical signs or symptoms of either DVT or PE (Table 2). The most common symptoms were edema or discomfort in the extremities. A similar number of outpatients (n = 2,725) and inpatients (n = 2,726) were registered. Among the inpatients, 2,118 (78%) had their DVT diagnosed while in nonintensive care units, and 605 (22%) had their DVT diagnosed while in intensive care units; 441 of the latter were on mechanical ventilation. The status of the remaining 3 patients is unknown.

Unilateral lower extremity DVT was detected in 77% of patients (n = 4,173), and bilateral lower extremity DVT was detected in 12% (n = 657). Of these patients, 829 (15.2%) had isolated calf DVT, and 1,988 (36.5%) had proximal and calf DVT. Upper extremity DVT was detected in 11% of patients (n = 604). In 17 patients (<1%), DVT was detected in other veins, including pelvic, neck, inferior vena cava, and portal.

For patients who had their DVT diagnosed while outpatients, the median time to diagnosis was 3 days after symptoms began; for those who had their DVT diagnosed while inpatients, the median time to diagnosis was 1 day. The most common admission diagnoses for inpatients who subsequently had their DVT diagnosed were infection (16%), cardiovascular disease (12%), neurologic disease (10%), and cancer (9%). The median length of hospital stay for those who had their DVT diagnosed while outpatients was 5 days; for those who had their DVT diagnosed while inpatients, it was 12 days ($p < 0.0001$). Of those who had their DVT diagnosed while outpatients, 80% (n = 2,176) were hospitalized for treatment of DVT (Table 3).

Overall, 71% of patients (n = 3,894)—including

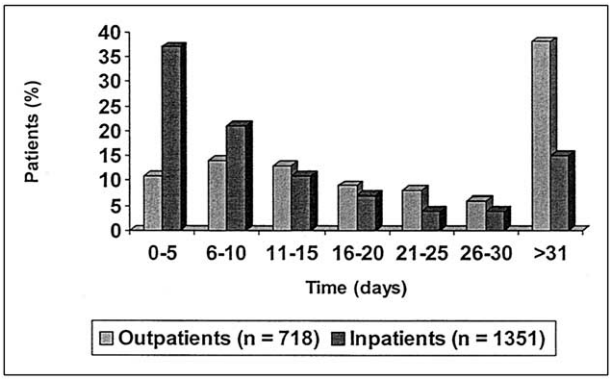

FIGURE 3. Time from most recent surgery to diagnosis of DVT by patient status at the time of DVT diagnosis. Data are missing for 25 patients.

TABLE 2 Signs and Symptoms of Deep Vein Thrombosis (DVT) by Patient Status at Time of Diagnosis

Signs and Symptoms of DVT/PE	Patient Status at Time of Diagnosis: Outpatient (n = 2,725)	Inpatient (n = 2,726)
None	41 (2%)	289 (11%)
Edema	2,241 (82%)	1,610 (59%)
Extremity discomfort	1,902 (70%)	1,000 (37%)
Dyspnea	363 (13%)	649 (24%)
Erythema	450 (17%)	224 (8%)
Difficulty walking	359 (13%)	174 (6%)
Chest pain	170 (6%)	230 (8%)
Cough	85 (3%)	132 (5%)
Syncope	23 (1%)	65 (2%)
Hemoptysis	16 (1%)	33 (1%)
Other	208 (8%)	253 (9%)

TABLE 3 Treatment Modalities for Current Deep Vein Thrombosis (DVT) by Inpatient and Outpatient Status

Treatment Modality	Patient Status at Time of Diagnosis: Outpatient (n = 2,725)	Inpatient (n = 2,726)
Subcutaneous low-molecular-weight heparin bridge to warfarin	1,244 (46%)	899 (33%)
Intravenous unfractionated heparin bridge to warfarin	1,071 (39%)	855 (31%)
Vena cava filter	235 (9%)	546 (20%)
Low-molecular-weight heparin monotherapy	152 (6%)	364 (13%)
Unfractionated heparin monotherapy	96 (4%)	230 (8%)
Warfarin	111 (4%)	145 (5%)
Unfractionated heparin bridge to low-molecular-weight heparin	108 (4%)	85 (3%)
Subcutaneous unfractionated heparin monotherapy	20 (1%)	137 (5%)
Thrombolytic therapy for DVT	27 (1%)	29 (1%)

2,295 nonsurgical patients (i.e., those with no history of surgery in the 3 months before diagnosis)—received no prophylaxis within 30 days before DVT was diagnosed. Of the 29% of patients (n = 1,557) who did receive prophylaxis, 410 had DVT diagnosed while outpatients and 1,147 while inpatients. The prophylaxis modality was pharmacologic in 60% (n = 931), mechanical in 20% (n = 309), combined pharmacologic and mechanical in 20% (n = 313), and unknown in 4 patients. For pharmacologic prophylaxis, 350 patients (38%) received low-dose unfractionated heparin, and 241 (26%) received low-molecular-weight heparin. Of the 2,726 who had DVT diagnosed while inpatients, 1,147 (42%) received prophylaxis within 30 days before diagnosis. Of the 787 patients who underwent surgery >14 days before DVT diagnosis, 376 (48%) received prophylaxis. Among prophylaxis recipients, 29% (n = 449) received unfractionated heparin and 15% (n = 241) received low-molecular-weight heparin. Prophylaxis with unfractionated heparin was 4 times more common in patients who had DVT diagnosed while inpatients versus outpatients (36% vs 9%, respectively).

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DVT FREE confirms that previous DVT, surgery, cancer, and immobility are the most common risk factors for DVT. Nonsurgical patients were much less likely to receive prophylaxis compared with surgical patients. In a multicenter, randomized double-blind trial of enoxaparin versus placebo in 1,102 hospitalized nonsurgical patients at risk for VTE, enoxaparin 40 mg/day decreased the VTE rate by 2/3 compared with placebo.[11] Nevertheless, routine preventive efforts were not widely practiced among inpatients enrolled in DVT FREE.

Almost all of the patients reported symptoms or signs of DVT before ultrasound confirmation. The more rapid diagnosis of DVT in inpatients may be related to closer observation, greater access to diagnostic ultrasound, or a higher index of suspicion compared with outpatients. The delay in diagnosis among outpatients may also possibly be caused by a variety of factors, such as difficulty in obtaining an appointment, lack of financial resources, or uncertainty regarding the potential medical importance of the symptoms.

Despite the American College of Chest Physicians' endorsement of outpatient therapy using low-molecular-weight heparin for acute DVT management[12], this approach was used in only 20% of patients.[13,14] This suggests that the improved efficacy and cost effectiveness of low-molecular-weight heparin, compared with unfractionated heparin, may not be generally appreciated or accepted.[15,16]

We were surprised by the high rate of vena caval filter implantation. Overall, 781 patients (14%) received filters: 235 were outpatients (9%) and 546 were inpatients (20%). The primary indication was "prophylaxis" for 257 of these 781 patients (33%). This raises the question of whether alternative forms of prophylaxis might be preferable because of excessive recurrent DVT [17] and rehospitalization rates[18] in patients with filters.

Two-thirds of the patients were either overweight (BMI 25 to 30 kg/m^2) or obese (BMI $\geq$30 kg/m^2).[19] In the Nurses' Health Study,[20] obesity was associated with a threefold increase in the likelihood of developing PE.

The validity of conclusions from registries depends on broad-based case ascertainment. Unlike randomized clinical trials, interpretation of registries should be limited to hypothesis generation.

APPENDIX

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