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Epidemiology

Upper-Extremity Deep Vein Thrombosis
A Prospective Registry of 592 Patients

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Background—Upper-extremity deep vein thrombosis (UEDVT) occurs spontaneously or sometimes develops as a complication of pacemaker use, long-term use of a central venous catheter (CVC), or cancer.

Methods and Results—To improve our understanding of UEDVT, we compared the demographics, symptoms, risk factors, prophylaxis, and initial management of 324 (6%) patients with central venous catheter (CVC)–associated UEDVT, 268 (5%) patients with non–CVC-associated UEDVT, and 4796 (89%) patients with lower-extremity DVT from a prospective US multicenter DVT registry. The non–CVC-associated UEDVT patients were younger (59.2 ± 18.2 versus 64.2 ± 16.9 years old; $P<0.0001$), less often white (65% versus 73%; $P<0.01$), leaner (body mass index [BMI] 26.8 ± 7.1 versus 28.5 ± 7.3 kg/m^2; $P<0.001$), and more likely to smoke (19% versus 13%; $P=0.02$) than the lower-extremity DVT patients. By way of propensity analysis and multivariable logistic regression analysis, we determined that an indwelling CVC was the strongest independent predictor of UEDVT (odds ratio [OR], 7.3; 95% confidence interval [CI], 5.8 to 9.2). An age of <67 years, a BMI of <25 kg/m^2, and hospitalization were the independent predictors of non–CVC-associated UEDVT. Most (68%) UEDVT patients were evaluated while they were inpatients. Only 20% of the 378 UEDVT patients who did not have an obvious contraindication to anticoagulation received prophylaxis at the time of diagnosis.

Conclusions—UEDVT risk factors differ from the conventional risk factors for lower-extremity DVT. Our findings identify deficiencies in our current understanding and the prophylaxis of UEDVT and generate hypotheses for future research efforts. (***Circulation***. 2004;110:1605-1611.)

Key Words: thrombosis ■ risk factors ■ prevention ■ anticoagulants

U pper-extremity deep vein thrombosis (UEDVT), which usually refers to thrombosis of the axillary or subclavian veins, occurs spontaneously or sometimes develops as a complication of pacemaker use, long-term central venous catheter (CVC) use, or cancer.[1–4] Historically, UEDVT was considered a benign and self-limited condition[5,6]; however, recent studies have demonstrated that UEDVT may have significant complications, including pulmonary embolism (PE), loss of vascular access, superior vena cava syndrome, and postthrombotic venous insufficiency.[7–10] Furthermore, the data that evaluate thrombosis risk with the newer catheter technologies are limited. To improve our understanding of UEDVT, we describe 592 patients with UEDVT from a prospective, US multicenter registry of 5451 patients with ultrasound-confirmed DVT.[11]

Methods

Patient Population
The objective of this study was to explore and compare the current epidemiology, prophylaxis, and initial management of UEDVT and lower-extremity DVT patients. We used the prospective US DVT Registry Database,[11] which enrolled 5451 consecutive patients with acute DVT from 183 urban, suburban, and rural study sites. The maximum enrollment period was 6 months (October 2001 to March 2002). Because this is a cross-sectional study, no long-term follow-up or primary or secondary end points were done or noted. We have data on the initial anticoagulation treatment strategies for these patients, which included (1) heparin or low-molecular-weight heparin (LMWH) as monotherapy or as a "bridge" to warfarin and (2) systemic or catheter-directed thrombolysis.

Comorbidities were defined a priori. The sole inclusion criterion was the confirmation of DVT by venous ultrasound examination. The original registry included no exclusion criteria. In this ancillary study, we excluded 63 patients (34 patients with simultaneous upper- and lower-extremity DVT and 29 patients with neither UEDVT nor lower-extremity DVT). UEDVT patients who received a CVC within 30 d of the DVT diagnosis were classified as having CVC-associated UEDVT. The remaining UEDVT patients were classified as having non–CVC-associated UEDVT.

In total, 4365 (80%) of the 5451 patients had at least 1 PE imaging test. PE was diagnosed if a high-probability ventilation-perfusion scan, positive contrast-enhanced spiral chest computed tomogram, contrast-enhanced magnetic resonance angiogram, or conventional contrast pulmonary angiogram was performed.

Data Collection

Data from patients with DVT diagnosed by venous ultrasound were obtained from medical records at each study site and recorded on case report forms by a study coordinator. Each site with more than 2 patients was monitored with at least 1 site visit by an independent auditor who confirmed the ultrasound diagnosis and reviewed the medical records to ensure accuracy. The interpretation of ultrasound readings was standardized. The primary criterion to diagnose DVT by ultrasound was noncompressibility of the vein; the secondary criterion was the absence of flow determined by Doppler ultrasound.[12–15]

Statistical Methods

The mean or median and frequency distribution were calculated for each continuous variable. We used analysis of variance (ANOVA) to assess for differences in means and the χ^2 statistic to assess for differences in proportions between the lower-extremity DVT group and the 2 UEDVT groups. When these tests were significant (2-tailed $\alpha < 0.05$), we conducted pairwise comparisons (contrasts for continuous variables and χ^2 tests for dichotomous variables) between the 2 UEDVT groups and between the non–CVC-associated UEDVT group and the lower-extremity DVT group. For these tests, we used a Bonferroni adjustment to correct for multiple comparisons and considered a 2-tailed $\alpha < 0.025$ significant. We did not compare the lower-extremity DVT patients to the CVC-associated UEDVT group because any differences between these two groups reasonably could be interpreted as differences between patients with a CVC and patients with lower-extremity DVT.

Because CVC use was not randomly assigned in this patient population, potential confounding and selection biases were addressed via propensity analysis.[16] The propensity for CVC use within 30 d of the venous thromboembolism (VTE) was determined without regard to DVT outcome using multivariable logistic regression analysis. A model was developed that contained 30 covariates including age; ethnicity; body mass index (BMI); smoking status; inpatient DVT diagnosis; personal or family history of VTE; major surgery or immobilization within 30 d; general anesthesia; cancer; ongoing radiation or chemotherapy; hypertension; diabetes; major gastrointestinal bleed, infection, or sepsis within 30 d; congestive heart failure; dialysis dependence; organ transplantation; and prophylaxis with warfarin, subcutaneous unfractionated heparin (UFH), intravenous UFH, or LMWH. A propensity score for CVC use was then calculated from the logistic equation for each patient. This score represented the probability that a patient received a CVC within 30 d of the VTE. The propensity scores were included in a second logistic regression analysis to determine the independent risk of CVC use within 30 d on the development of UEDVT.

After excluding the CVC-associated UEDVT group, we also performed multivariable logistic regression analysis to identify factors that predict non–CVC-associated UEDVT rather than lower-extremity DVT. Univariately significant variables ($P < 0.05$) between the non–CVC-associated UEDVT and lower-extremity DVT groups were entered into the model. All statistical comparisons were performed by Quintiles Inc. using SAS version 6.12 (SAS Institute Inc).

Results

Patient Demographics

Of the 5388 patients evaluated, 592 (11%) had UEDVT (292 women, 300 men) and 4796 patients (89%) had lower-extremity DVT (2567 women, 2229 men). We found 324 UEDVT patients (55%) with CVC-associated DVT and 268 patients (45%) with non–CVC-associated UEDVT. The 2 UEDVT groups were similar with regard to age, gender, ethnicity, BMI, and smoking status (Table 1). The non–CVC-associated UEDVT patients were younger (Figure 1), less often white and more often African American, leaner (Figure 2), and more likely to smoke (independent of the presence of lung cancer) than the lower-extremity DVT patients.

Presentation of DVT

The 2 UEDVT groups presented with similar symptoms, except for extremity discomfort and dyspnea, which were reported more frequently by the non–CVC-associated UEDVT group (Table 1). The non–CVC-associated UEDVT patients presented more frequently with edema (79% versus 69%; $P = 0.001$) than did the lower-extremity DVT patients, but less commonly with extremity discomfort (46% versus 55%; $P < 0.01$), dyspnea, or chest pain. Using log-linear tests of homogeneous association and tests of conditional independence, we found that the non–CVC-associated UEDVT patients were more likely to present with extremity edema even after controlling for cancers that were likely to cause lymphatic obstruction or vessel compression, such as breast or respiratory/oral neoplasms.

A similar proportion of patients in the 2 UEDVT groups had PE; however, PE was found less frequently in the UEDVT patients than in the lower-extremity DVT group (3% versus 16%; $P < 0.001$). PE was confirmed in 8 of 49 (16%) UEDVT patients with dyspnea, 2 of 18 (11%) UEDVT patients with chest pain, and 1 of 4 (25%) UEDVT patients with syncope.

Compared with the lower-extremity DVT patients, the UEDVT patients were more frequently evaluated during hospitalization, especially when the UEDVT was CVC associated (Table 1). The median duration of hospitalization from admission to DVT diagnosis was 9 and 5 d in the CVC-associated and non–CVC-associated UEDVT groups, respectively ($P < 0.0001$), and 3 days in the lower-extremity DVT patients.

Risk Factors

A similar proportion of patients in the 2 UEDVT groups presented with cancer or a personal or family history of VTE (Table 2); however, major surgery within 30 d, a history of immobilization within 30 d, and ongoing chemotherapy were more frequent covariates in the CVC-associated UEDVT group.

Compared with the lower-extremity DVT patients, the non–CVC-associated UEDVT group was less likely to have a personal history of VTE (19% versus 30%, $P < 0.0001$), less likely to have undergone major surgery within the preceding 30 d (11% versus 17%, $P < 0.01$), and more likely to be receiving ongoing chemotherapy (15% versus 10%; $P < 0.01$). Irradiation to the chest and axillae did not appear to differ between these groups because a similar proportion of patients were receiving radiation therapy for breast, respiratory/oral, and blood/lymphatic/cardiovascular cancers.

With multivariable logistic regression analysis, the most powerful independent predictor of UEDVT was the presence of an indwelling CVC (adjusted odds ratio [OR], 9.7; 95% confidence interval [CI], 7.8 to 12.2). The C statistic for the propensity score model was 0.83, indicating excellent discrimination between the patients who received a CVC within 30 d and patients who did not. Every 0.1-unit increase in propensity score was associated with a 1.16-

TABLE 1. Baseline Characteristics of Patients With DVT

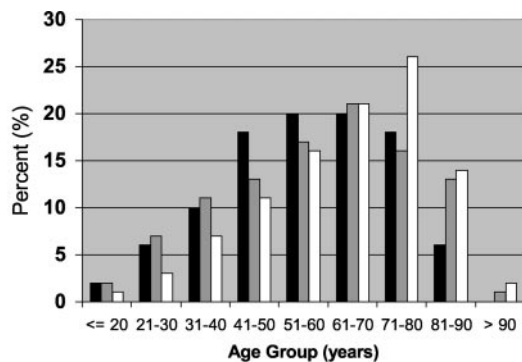| | UEDVT (n=592) | | | | |
| | CVC Within 30 d | | | | |
Characteristic	Yes (n=324)	No (n=268)	P*	Lower-Extremity DVT (n=4796)	P†
Age, y	57.2±16.3	59.2±18.2	0.20	64.2±16.9	<0.0001
Men, %	50	51	...‡	46	...
Ethnicity, %					
White	63	65	0.69	73	<0.01
African American	26	22	0.36	16	<0.01
Hispanic	4	5	...	4	...
Other/unknown	7	8	...	7	...
BMI, kg/m^2	26.3±6.5 (n=266)	26.8±7.1 (n=216)	0.49	28.5±7.3 (n=3906)	<0.001
Current smoker, %	17	19	0.53	13	0.02
DVT diagnosed while inpatient, %	75	59	<0.0001	48	<0.001
Signs/symptoms, %					
None	5	6	...	6	...
Swelling	82	79	0.35	69	0.001
Extremity discomfort	37	46	0.02	55	<0.01
Erythema	13	15	...	12	...
Dyspnea	6	11	0.02	20	<0.001
Chest pain	3	3	0.94	8	<0.01
Cough	1	3	0.22	4	0.19
Syncope	1	1	...	2	...
Other	10	11	...	8	...
Confirmed PE	3	2	0.35	16	<0.0001

Plus-or-minus values are mean±SD.
*Compares UEDVT groups.
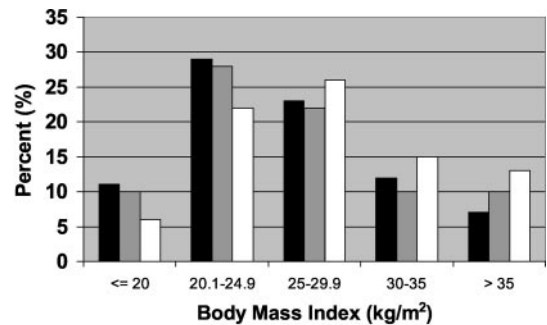†Compares non–CVC UEDVT and lower-extremity DVT groups.
‡Nonsignificant ANOVA.

fold higher OR (95% CI, 1.10 to 1.22; $P<0.0001$) of developing upper-extremity rather than lower-extremity DVT. CVC use within 30 d preceding the VTE was associated with a 7.30-fold higher OR (95% CI, 5.79 to 9.21; $P<0.0001$) of upper-extremity rather than lower-extremity DVT after the propensity score was introduced into the model.

In another multivariable logistic regression analysis, an age of <67 years (median age for the subset of patients with either lower-extremity DVT or non–CVC-associated upper-extremity DVT), a BMI of <25 kg/m^2, and hospitalization were independent predictors of non–CVC-associated UEDVT (Figure 3). In contrast, major surgery within 30 d and a personal history of DVT predicted

Figure 1. Distribution of DVT patients by age.

Figure 2. Distribution of DVT patients by BMI.

TABLE 2. Risk Factors for DVT

Risk Factor	UEDVT (n=592) CVC Within 30 d Yes (n=324)	No (n=268)	P*	Lower-Extremity DVT (n=4796)	P†
History of PE, %	5	2	0.09	7	<0.01
History of DVT, %	16	17	0.77	23	0.04
Family history of VTE, %	2	3	0.69	5	0.08
Major surgery within 30 d, %	23	11	<0.0001	17	<0.01
Gastrointestinal	10	4	<0.01	4	0.40
Cardiovascular	6	2	0.04	2	0.92
Neurological	3	1	…‡	3	…
Post-trauma	<1	1	…	2	…
Hip or knee	1	<1	1.00	3	<0.01
Immobilization within 30 d	44	29	<0.0001	34	0.07
General anesthesia, %	36	19	<0.0001	20	0.73
Cancer, %	42	36	0.20	32	0.11
Gastrointestinal	10	6	0.08	4	0.05
Genitourinary	6	14	<0.01	5	<0.0001
Respiratory/oral cavity	7	4	0.23	9	0.01
Breast	7	6	0.83	5	0.14
Blood/lymphatic/cardiovascular	11	5	<0.01	7	0.20
Active cancer,§ %	30	24	0.10	19	0.05
Ongoing radiation therapy	6	6	0.98	3	0.03
Chest wall/axilla radiation‖	3	1	0.20	1	1.00
Ongoing chemotherapy	24	15	<0.01	10	<0.01
CVC, %	100			10	
Neck	25			3	
Upper extremity	51			3	
Chest	24			3	
Major trauma, %	3	1	0.29	3	0.09
Women's health, %					
No. of women	50	49	…	54	…
Hormone replacement therapy	11	12	…	14	…
Pregnant or postpartum	4	1	…	2	…
Hormonal contraceptives	3	5	…	4	…

*Compares UEDVT groups.

†Compares non-CVC UEDVT and lower-extremity DVT groups.

‡Nonsignificant ANOVA.

§Active cancer, cancer diagnosis within 6 months, or ongoing radiation and/or chemotherapy.

‖Respiratory/oral, blood/lymphatic/cardiovascular, or breast cancer patients receiving ongoing radiation therapy.

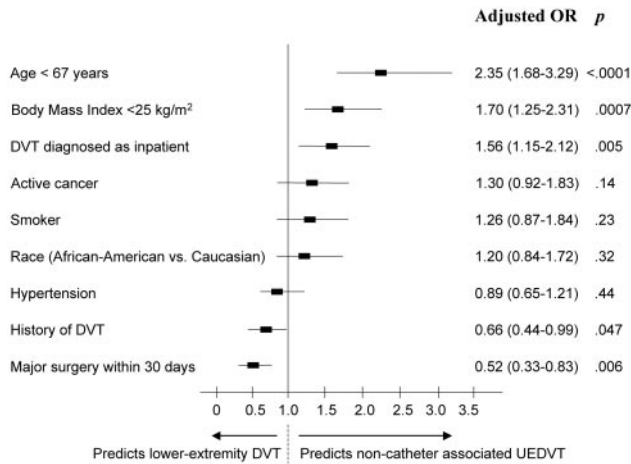lower-extremity DVT rather than non–CVC-associated UEDVT.

Comorbidities

The most frequent comorbidities in the 2 UEDVT groups were hypertension, diabetes mellitus, neurological disease, and nonpulmonary infection within 30 d (Table 3). Compared with the CVC-associated UEDVT group, fewer patients in the non–CVC-associated UEDVT group presented with nonpulmonary infection, sepsis, and major gastrointestinal bleeding within 30 d. Dialysis dependence and organ transplantation were more commonly found in the non–CVC-associated UEDVT group than in the lower-extremity DVT group.

Treatment of DVT

Most patients were treated with LMWH monotherapy without warfarin or LMWH or UFH as a "bridge" to long-term warfarin therapy. The initial treatment strategies did not differ between the 2 UEDVT groups or between the non–CVC-associated UEDVT group and the lower-extremity DVT group. Catheter-directed and systemic thrombolysis for DVT was rarely used, implemented in only 10 (3%) CVC-associated UEDVT patients, 10 (4%) non–CVC-associated UEDVT patients, and 53 (1%) lower-extremity DVT patients (P=0.002 for non-CVC UEDVT versus lower-extremity DVT).

Figure 3. Multivariable logistic regression analysis to identify factors predicting non–CVC-associated UEDVT rather than lower-extremity DVT.

Prophylaxis of DVT

Fewer non–CVC-associated UEDVT patients received pharmacological prophylaxis within the 30 d preceding the VTE than did the CVC-associated UEDVT group (25% versus 40%; $P<0.0001$) (Table 4). A similar proportion of the lower-extremity DVT patients and non–CVC-associated UEDVT patients received pharmacological prophylaxis; however, only 20% of the 378 UEDVT patients who did not demonstrate an obvious contraindication to anticoagulation (ie, not receiving chemotherapy and no major surgery within 30 d) were receiving prophylaxis at the time of the VTE. Warfarin, subcutaneous UFH, and LMWH were the most common prophylaxis regimens, used in 14%, 10%, and 8% of UEDVT patients, respectively.

Discussion

This large registry provides a contemporary profile of patients diagnosed with UEDVT throughout the United States and highlights several important similarities and differences between UEDVT and lower-extremity DVT patients. A similar proportion of patients with lower-extremity DVT and non–CVC-associated UEDVT had a history of cancer; however, cancer was found most frequently in the CVC-associated UEDVT group. This finding is consistent with previous studies, which demonstrated that the placement of a CVC in patients with coexisting cancer is a potent stimulus for UEDVT.[17]

Overall, the most powerful independent predictor of UEDVT was the presence of a CVC, which increased the odds of UEDVT $\approx$7-fold. This effect estimate was based on a propensity analysis that provided a more rigorous adjustment for selection bias than would be achieved with standard multivariable analysis. After excluding the subset of patients with CVC-associated UEDVT, we also found that several conventional risk factors for lower-extremity DVT such as surgery, advancing age, and obesity did not predispose to non–CVC-associated UEDVT. Rather, younger age, lean body weight, and inpatient status independently predicted non–CVC-associated UEDVT. These findings support UEDVT prophylaxis trials for young lean inpatients with a CVC because these individuals may be at highest risk for UEDVT.

Inpatients may be at a higher risk for UEDVT than outpatients because acute illness requiring hospitalization or the almost universal use of peripheral intravenous catheters and intravenous medications during hospitalization may predispose them to thrombosis. Alternatively, hospitalization provides a setting where physicians may be more likely to note subtle abnormalities on physical examination or recog-

TABLE 3.   Comorbidities in Patients Diagnosed with DVT

| Comorbidity | UEDVT (n=592) | | | Lower-Extremity DVT (n=4796) | P† |
| | CVC Within 30 d | | | | |
	Yes (n=324)	No (n=268)	P*		
Hypertension, %	46	44	0.57	50	0.03
Diabetes mellitus, %	26	22	0.29	20	0.48
Neurological disease, %	22	18	…‡	22	…
Nonpulmonary infection <30 d, %	23	11	0.0001	9	0.35
Congestive heart failure, %	14	16	0.46	12	0.07
Chronic obstructive pulmonary disease, %	10	16	…	12	…
Dialysis dependent, %	14	9	0.09	2	<0.0001
Sepsis <30 d, %	16	6	<0.0001	4	0.07
Bronchitis or pneumonia <30 d, %	14	9	0.06	8	0.78
Organ transplantation, %	7	4	0.08	1	<0.01
GI bleed requiring transfusion <30 d, %	6	2	0.01	2	0.56
Stroke <30 d, %	2	3	…	3	…

*Compares UEDVT groups.
†Compares non-CVC UEDVT and lower-extremity DVT groups.
‡Nonsignificant ANOVA.

TABLE 4. Prophylactic Measures Within 30 d Before VTE

| | UEDVT (n=592) | | | | |
| | CVC Within 30 d | | | | |
Prophylaxis	Yes (n=324)	No (n=268)	P*	Lower-Extremity DVT (n=4796)	P†
Pharmacologic prophylaxis, %	40	25	<0.0001	27	0.34
Warfarin, %	15	13	…‡	13	…
Subcutaneous UFH, %	12	8	0.10	7	0.30
Low molecular weight heparin, %	12	3	<0.001	7	0.02
IV UFH, %	6	3	0.11	3	0.96
UFH via any route, %	17	12	0.05	10	0.31
Vena cava filter, %	3	3	…	4	…

*Compares UEDVT groups.
†Compares non-CVC UEDVT and lower-extremity DVT groups.
‡Nonsignificant ANOVA.

nize potential symptoms of UEDVT. These theories are speculative and cannot be tested by using the available data from the present study.

In this registry, only 20% of the UEDVT patients with no obvious contraindication to anticoagulation received prophylaxis at the time of the VTE. Furthermore, 26% of the UEDVT patients who received pharmacological prophylaxis within 30 d before the VTE event were given subcutaneous UFH, which, unlike low-dose warfarin or LMWH, has not been shown to reduce the risk of UEDVT.[18–20] The omission of prophylaxis and the inappropriate use of prophylaxis across varied practice settings suggest the need for systems changes that address these issues.

Our methodology is consistent with published criteria for judging the scientific value of a clinical data registry.[21] Consecutive patients with ultrasound-confirmed DVT were enrolled from many urban, suburban, and rural study sites throughout the United States. A steering committee was responsible for overseeing the study. Institutional review board approval was obtained.[11] The interpretation of ultrasound readings was standardized using the well-established criteria of noncompressibility of the vein and absence of flow.[11–15] An independent auditor confirmed the ultrasound diagnosis and reviewed medical records to ensure accuracy at study sites with >2 participants. Professional statisticians performed the data analyses.[11]

The diagnosis of DVT in this study was based solely on ultrasonography. Although this technique has excellent sensitivity and specificity for proximal lower-extremity DVT, ultrasonography has lower sensitivity (78% to 100%) and specificity (82% to 100%) for UEDVT because acoustic shadowing from the clavicle and sternum limits visualization of the proximal upper-extremity veins.[8,22,23] The lower specificity may have resulted in misdiagnosis of UEDVT in up to 18% of the UEDVT patients. Also, we have information on CVC use only during the 30 d before the VTE. Therefore, some patients classified as having non-CVC UEDVT may have had a CVC removed >30 d before the index event. These factors may have contributed to some of the differ-

ences between the lower-extremity DVT and the non–CVC-associated UEDVT patients.

We have no data on outcomes or CVC characteristics, such as catheter make, lumen diameter, insertion site, tip location, or medication infused. These CVC characteristics may alter UEDVT risk.[17] Additionally, the rate of thrombosis with older CVC technologies may differ substantially from the newer technologies used in the present study.[17,24]

Our registry probably underestimated the true rate of PE because PE imaging tests were not performed or were inconclusive in 20% of the registry patients. Because PE was not diagnosed in most patients with dyspnea, chest pain, or syncope, it is likely that these symptoms were caused by comorbidities such as heart disease, lung disease, infection, or cancer. In addition, symptoms may originate from the UEDVT itself.

In summary, many factors associated with UEDVT differ from the conventional risk factors for lower-extremity DVT. The lack of familiarity with these unique aspects and with appropriate prophylaxis regimens may partly explain why most patients at risk for UEDVT in the United States do not receive effective prophylaxis. This study identifies the deficiencies in our current understanding and prophylaxis of UEDVT. These problems require urgent action. Our report should provide an impetus for reform and should generate hypotheses for future research.

Acknowledgments

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