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Venous Thromboembolism in the Elderly: A Community-Based Perspective

Frederick A. Spencer, MD^{*,†}, Joel M. Gore, M.D.[†], Darleen Lessard, MS[†], Cathy Emery, RN[†], Luigi Pacifico, D.O.[‡], George Reed, PhD[†], Jerry H. Gurwitz, M.D.[†], and Robert J. Goldberg, PhD[†]

^{*} Department of Medicine, McMaster University Medical Center, Hamilton, Ontario

[†] Department of Medicine, University of Massachusetts Medical School, Worcester, MA

[‡] Department of Medicine, Fallon Community Health Care, Worcester, Ontario

SUMMARY

Background: While the magnitude of venous thromboembolism (VTE) increases dramatically with advancing age, relatively little is known about the contemporary management of VTE in the elderly and the impact of age on associated short and long-term outcomes.

Objectives: The objectives of this population-based study were to compare the clinical characteristics, treatment practices, and outcomes of subjects ≥ 65 years with VTE to those of younger patients.

Patients/Methods: The medical records of residents of the Worcester (MA) metropolitan area with ICD-9 codes consistent with VTE during 1999, 2001, and 2003 were independently validated and reviewed by trained data abstractors. Information about patients' demographic and clinical characteristics, hospital management practices, and hospital and long-term outcomes was collected.

Results: There were a total of 1,897 validated events of VTE - 1,048 (55%) occurred in patients ≥ 65 years of age. Patients ≥ 65 years were less likely to have “unprovoked” VTE than younger patients. They were less likely to receive parenteral anticoagulation or warfarin as acute treatment. Rates of recurrent VTE did not differ significantly between patients 65 years of age or older compared to younger patients but the adjusted rates of major bleeding were increased approximately 2-fold in older patients.

Conclusion: Advancing age is not a predictor of recurrent VTE but is associated with a significant increase in major bleeding episodes. Physicians treating elderly patients with VTE should continue to base their decisions on clinical characteristics previously shown to impact the risk of recurrent VTE. These decisions must be tempered by our observation that major bleeding occurs frequently in these patients.

Keywords

aging; bleeding; elderly; venous thromboembolism

Introduction

Venous thromboembolism (VTE), comprising the conditions of deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cardiovascular disorder in adult Americans. While the magnitude of VTE increases dramatically with advancing age, relatively little is known about the natural history of this disorder in the elderly. The high-risk elderly population has unfortunately been under-represented in clinical trials evaluating therapeutic options for this condition, thereby leaving clinicians to generalize resulting data to the elderly when making clinical decisions. The contemporary management of VTE in the elderly and associated short and long-term outcomes is not known.

The objectives of the Worcester Venous Thromboembolism study are to provide contemporary population-based data about the clinical epidemiology of venous thromboembolism as well as its management and associated outcomes among residents of a large New England metropolitan area [1]. The purpose of the present investigation was to characterize differences in the incidence rates, clinical course, management practices, and outcomes of VTE in the elderly (≥ 65 years) compared to younger patients with VTE.

Methods

Computerized printouts of residents of the Worcester (MA) metropolitan area with healthcare system encounters in which any of 34 ICD-9 diagnosis codes possibly consistent with the occurrence of VTE had been listed in 1999, 2001, and 2003 were obtained from each of the 12 hospitals serving residents of the Worcester Standard Metropolitan Statistical Area (SMSA) [1]. These data queries were not limited to discharge diagnoses, but also encompassed all outpatient, emergency department, radiology, and laboratory encounters.

The medical records of all identified patients meeting the geographic inclusion criteria (residents of the Worcester SMSA, 2000 census = 477,800) were reviewed [1]. Trained nurse abstractors using pre-specified criteria performed the validation and characterization of each case of VTE as being definite, probable, possible, or absent [1]. These criteria were based on a modification of a classification schema proposed by Silverstein et al [2]. Each case and its classification were also validated by the study project coordinator (CE). If the classification of VTE was not immediately apparent using the diagnostic criteria specified, the medical record was further reviewed by the principal investigator (FS). Incident cases of VTE were defined as those occurring in patients without any prior history of upper or lower extremity DVT or PE. Potential cases of recurrent VTE were classified using similar criteria as that employed for incident cases; the development of a probable or definite recurrence of VTE required the new occurrence of thrombosis in a previously uninvolved venous or pulmonary vessel by ultrasound or radiologic imaging.

Data collection

Information was collected about patients' demographic characteristics, medical history, clinical characteristics, diagnostic test results, and hospital management practices through review of the medical record. Only medical history variables documented in patients' medical records by a physician were abstracted. The surgery variable included major operations where general or epidural anesthesia lasted 30 minutes or longer. Medical history variables defined as "recent" were those occurring or active in the 3 months prior to the diagnosis of VTE. Major bleeding was defined as any episode of bleeding requiring transfusion or that resulted in subsequent hospitalization, stroke, myocardial infarction, , or death. Subjects were considered to have malignancy-related VTE if they had malignancy (other than basal cell skin cancer) that was being treated or palliated at the time of VTE diagnosis. "Provoked" VTE was defined as VTE occurring within 3 months of hospitalization, major surgery, pregnancy, trauma, or fracture.

“Unprovoked” VTE was defined as VTE occurring in the absence of malignancy or any of the above “provoked” variables.

The development of a first recurrence of VTE or a major bleeding episode were determined through the review of subsequent medical records at the same hospital site as the index event as well as through the screening of medical records from the other participating hospital sites. Information about all cause mortality was obtained through hospital record reviews and review of death certificates at the Massachusetts Division of Vital Statistics. Follow-up data were available for a maximum of 3 years.

Data Analysis

Incidence rates of initial as well as all episodes of DVT and PE, further stratified according to age, were calculated based on U.S. census estimates of the greater Worcester population in 2000. Differences in the distribution of demographic and clinical characteristics as well as treatment practices in patients further stratified according to age were examined using chi-square tests of statistical significance for categorical variables (Mantel-Haenszel for trend) and ANOVA for continuous variables. Cumulative incidence rates of VTE recurrence, major bleeding, (censoring subjects at the time of death) as well as all-cause mortality were estimated using the life-table method.

Cox regression analyses were constructed in order to evaluate whether age at the time of VTE presentation was associated with our pre-specified outcomes during follow-up including occurrence of recurrent VTE, recurrent VTE manifested as PE, major bleeding, and all-cause mortality. All variables listed in Tables 2 and 3 were included as controlling factors in our regression models. The occurrence of recurrent VTE was included in the analysis of major bleeding as a time-dependent variable in order to assess the impact of this complication on this study outcome. Similarly, the occurrence of major bleeding was included in the analysis of recurrent PE as a time-dependent variable. Finally, the occurrence of new or recurrent PE, any recurrent VTE, and major bleeding were included in our analyses of the relation of age with all-cause mortality.

Results

Incidence rates of venous thromboembolism

The age-adjusted and age-specific incidence rates of VTE (initial and overall cases of DVT, upper extremity DVT, isolated calf vein DVT, PE with or without DVT, and any VTE) are shown in Table 1. There were a total of 1,897 validated events of VTE yielding an overall age-adjusted attack rate of 138/100,000 population. The incidence rates of initial and total VTE increased markedly with advancing age. Similar age-related increases were noted for each subcategory of VTE type.

Demographic and clinical characteristics

The demographic and clinical characteristics of patients with VTE, further stratified according to age, are shown in Table 2. Patients 65 years and older with VTE were more likely to female, have cancer, have been recently hospitalized, have had a severe infection heart failure, or have undergone a cardiac procedure than younger patients. Older individuals were less likely to have unprovoked VTE and were less likely to have received a recent central venous catheter.

We also examined differences in these characteristics in 4 age strata for purposes of more systematically exploring the relation of older age with these characteristics: < 65 years, 65-74 years, 75-84 years, and aged 85 years or older (Table 2). With increasing age the frequency of subjects with VTE who were female or who had had a recent hospitalization or fracture

increased. The frequency of a recent central venous catheter or presentation with an unprovoked VTE declined with increasing age. Finally, the frequency of a number of clinical characteristics increased from age < 65 years to age 65-74 years but declined thereafter (recent surgery, recent malignancy, recent hormonal therapy, recent chemotherapy) such that patients age 85 years or older were least likely to have these characteristics.

Acute treatment practices

Patients 65 years and older were less likely to receive some form of parenteral anticoagulation or warfarin as acute treatment for their VTE as compared to patients < 65 years of age (Table 3). On the other hand, older patients with VTE were more likely to have an IVC filter implanted as part of their management in comparison to younger patients.

Short and long-term outcomes

VTE recurrence—Outcomes over a 3-year follow-up period, further stratified according to age, are displayed in Table 4 and Figures 1 to 3. The rates of clinically recognized recurrent or new PE or recurrent VTE did not significantly differ between patients 65 years and older compared to younger patients (Table 4). Similarly, the rates of recurrent VTE did not significantly differ between our 4 age subgroups (Figure 1).

After Cox regression modeling, the occurrence of major bleeding following a diagnosis of VTE (HR 3.18, 95% CI 1.83, 5.54) was the only predictor of recurrence of VTE during our 3-year follow-up period (Table 5). Patients $\geq$ 65 years of age were less likely to develop a recurrent episode of VTE than younger patients (HR 0.58, 95% CI 0.38, 0.90). Repeating our Cox regression analyses in patients $\geq$ 65 years into separate age strata also revealed either a significantly decreased risk, or trend towards a decreased risk, of VTE recurrence in each cohort (age 65-74 years: HR 0.58, 95% CI 0.32, 1.03; age 75-84 years: HR 0.68, 95% CI 0.40, 1.17; age $\geq$ 85 years: 0.42, 95% CI 0.20, 0.88) relative to patients less than 65 years old.

We also conducted similar Cox regression analyses, separately in patients < 65 years and in those $\geq$ 65 years, for purposes of determining whether factors associated with recurrent episodes of VTE differed between these two cohorts. The only predictor of recurrent VTE in either cohort was development of major bleeding (<65 years: HR 3.04, 95% CI 1.21, 7.65; $\geq$ 65 years: HR 3.56, 95% CI 1.65, 7.67).

Major bleeding episodes—The incidence rates of major bleeding episodes were approximately 2 times greater in patients age 65 years and older than in younger patients at all time points examined (Table 4). The frequency of major bleeding episodes also increased with age within our four age strata (figure 2). Slightly more than 50% of all major bleeding episodes occurred within 1 month of the diagnosis of VTE.

After Cox regression analysis, age $\geq$ 65 years was associated with the occurrence of major bleeding during our 3-year follow-up (HR 1.71, 95% CI 1.05, 2.76; referent group = patients <65 years of age) (Table 5). Repeating our Cox regression analyses in different strata of those $\geq$ 65 years suggested an increased risk of bleeding with increasing age (age 65-74 years: HR 1.42, 95% CI 0.77, 2.60; age 75-84 years: HR 1.89, 95% CI 1.08, 3.33; age $\geq$ 85 years: 2.05, 95% CI 1.00, 4.17). In Table 5 we also present data on additional predictors of major bleeding events over our 3-year follow-up period.

We also conducted Cox regression analyses using the same covariates, separately in patients < 65 years and in those $\geq$ 65 years, to determine if predictors of bleeding varied between these groups. Predictors of bleeding in patients <65 years included a recent ICU discharge (HR 4.84, 95% CI 1.51, 15.51), isolated DVT as an incident event (as compared to PE +/- DVT) (HR

2.51, 95% CI 1.12, 5.60), acute treatment with unfractionated heparin (HR 2.70, 95% CI 1.09, 6.69), and occurrence of a recurrent VTE event (HR 3.39, HR 1.02, 11.31). Predictors of bleeding in patients ≥ 65 years included female sex (HR 1.87, 95% CI 1.02, 3.43), acute treatment with low-molecular weight heparin (HR 2.75, 95% CI 1.33, 5.68), and occurrence of a recurrent VTE event (HR 3.92, 95% CI 1.58, 9.75).

All-cause mortality—All-cause death rates were increased at all time points examined in patients 65 years and older compared to patients < 65 years of age. These death rates also increased with advancing age in our older age strata (Table 4, figure 3). After Cox regression analysis, age ≥ 65 years was the strongest predictor of mortality during our 3-year follow-up (HR 2.31, 95% CI 1.60, 3.34). In Table 5 we also present data for other predictors of mortality over the 3-year follow-up period. In a repeat Cox regression analysis including only patients ≥ 65 years, occurrence of major bleeding following a diagnosis of VTE was associated with increased mortality (HR 2.75, 95% CI 1.77, 4.26). However, recurrent VTE was not associated with increased mortality in this elderly cohort (HR 0.72, 95% CI 0.43, 1.28).

Discussion

In this population-based study of residents of a large new England metropolitan area, the incidence rates of VTE increased markedly with advancing age – from 71/100,000 population in persons < 65 years to 885/100,000 population in those 85 years and older. Patients 65 years and older comprised more than one-half of all cases of VTE occurring in greater Worcester residents. This study also offers important insights into the relationship between age, VTE, and severally clinically relevant short and well as long-term outcomes.

Recurrent VTE

While ours and other studies have noted a marked increase in the incidence rates of VTE with advancing age, the impact of age on the risk of recurrent VTE has not been clearly elucidated [1,3,4]. In a population-based study of residents of Rochester, MN, diagnosed with VTE between 1966 and 1990, the risk of overall VTE recurrence increased by 17% per decade increase in age at the time of the initial episode of VTE [5]. On the other hand, in a retrospective study of more than 36,000 California residents admitted with or developing acute DVT during hospitalization from 1991 to 1994, there was a 15% reduction in the incidence rates of recurrent VTE per increasing decade of life [6].

In our study, the rates of a recurrent episode of VTE were similar in elderly patients as in younger patients at all time points examined. Since patients who died were censored from further analysis, this finding does not reflect a survival bias. As such, advanced age alone is not an indication for prolonged duration of warfarin therapy. In fact, a large proportion of elderly patients with VTE were likely to have one or more transient risk factors for VTE (e.g. hospitalization, infection, fracture, heart failure). Given the lower risk of recurrence with “provoked” VTE [7], one would anticipate that many elderly patients are eligible for short treatment courses (e.g. 3 months).

Major Bleeding

On the other hand, the frequency of major bleeding episodes was increased approximately two-fold over our 3-year follow-up period in the elderly as compared to younger patients. In fact, major bleeding occurred more frequently than recurrent VTE at 30 days and 1 year in patients greater than 65 years of age. The rates observed in our study are between 3-4 fold higher than those observed in recent trials of VTE therapy [8-10]. It is noteworthy that more than 50% of the major bleeding events occurred relatively soon (within 1 month) after the diagnosis of VTE. Similar findings were reported from the RIETE (Registro Informatizado de la Enfermedad

TromboEmbolica) registry in which subjects > 80 years of age had a 1.7 fold increased risk of major bleeding during 3 month follow-up compared to subjects < 80 years (11). These findings highlight the inherent difficulties with anticoagulation in elderly patients with VTE (particularly in the acute setting), many of whom have recently undergone hospitalization, invasive procedures, or surgery. Moreover, in our study the occurrence of major bleeding was the strongest predictor of subsequent episodes of VTE. One possible explanation for these findings is that the occurrence of major bleeding leads to an interruption of anticoagulation therapy, which may predispose to recurrent VTE.

Clearly, better anticoagulation strategies are needed in the elderly. Numerous studies have suggested that older patients have an increased risk of heparin-induced bleeding [12-14]. Nevertheless, unfractionated heparin was utilized in approximately half of the elderly patients receiving acute anticoagulant therapy in our study. Similarly, the utilization of warfarin in the elderly is particularly problematic given its narrow therapeutic index, prolonged effect, and susceptibility to drug and other environmental interactions. Numerous studies have identified age as an independent risk factor for the occurrence of major bleeding episodes during warfarin therapy [15-19]. In a multi-center inception cohort study of patients treated with warfarin for atrial fibrillation, major bleeding occurred in approximately 5% of patients >75 years compared to approximately 1% of younger patients [19]. In this study, older age was the only variable independently associated with an increased risk of bleeding.

Existing and novel alternatives to warfarin treatment require further study in elderly patients with VTE. There are a number of promising oral anticoagulants currently in development (e.g., oral antithrombin or Xa antagonists) though their long-term effectiveness remains unknown (20). Given the high incidence of VTE in the elderly, as well as specific age-related problems in treatment (e.g. renal disease, concomitant medications), Phase III studies of these agents for the prevention and treatment of VTE should be conducted, specifically in the elderly. At the very least, such studies should be designed to ensure proper enrollment of elderly men and women.

Study limitations

Similar to the design and conduct of any observational study, the present investigation has several limitations. The most significant limitation of our study is that we do not have information on patients' long-term treatment with anticoagulation. The vast majority of patients were treated acutely with anticoagulation and our experience is that most will be discharged on anticoagulation barring a bleeding episode. Nevertheless, we cannot comment on the timing, intensity, or type of therapy and its relationship to the development of recurrent VTE or bleeding. As such, we can only hypothesize about the impact of use of various anticoagulation strategies on our observed study outcomes. Although we conducted a broad screening for all possible cases of VTE in the greater Worcester population, we cannot claim complete case ascertainment of index VTE events, episodes of VTE recurrence, or episodes of major bleeding. To the extent that collection of these data may have varied according to patient age, some bias may have been introduced into our study. We also acknowledge that misclassification of some cases of VTE as unprovoked may have occurred due to suboptimal documentation of recent provoking factors (e.g. same-day surgery) in the medical record. Finally, due to the extremely low autopsy rates during the period under study, we are unable to estimate the rates of fatal PE. Therefore, we can only comment on complication rates and mortality associated with clinically recognized VTE.

Conclusions

Patients 65 years and older constitute the majority of cases of VTE in the community setting. Advancing age does not appear to be a predictor of recurrent VTE but is associated with a significant increase in major bleeding episodes. As such, physicians treating elderly patients with VTE should continue to base their decisions on clinical characteristics previously shown to impact the risk of recurrent episodes of VTE (e.g., unprovoked vs. provoked VTE, presence or absence of malignancy). These decisions must be tempered by our observation that major bleeding occurs frequently in these patients and that the occurrence of bleeding was one of the strongest predictors of recurrent VTE. Given these issues, it is clear that existing and novel alternatives to current VTE treatment strategies require further study in elderly patients.

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Figure 1.
Cumulative rate of recurrent VTE stratified by age

Figure 2.
Cumulative rate of major bleeding episodes stratified by age

Figure 3.
Cumulative mortality rate stratified by age

Table 1
Age-Specific Incidence and Attack Rates of Venous Thromboembolism: The Worcester Venous Thromboembolism Study

	Total VTE	Initial VTE	Total DVT	Initial DVT	Total PE	Initial PE	Upper Extremity DVT	Isolated Calf DVT
# of Events	N = 1,897	N = 1,567	N = 1592	N = 1,310	N = 545	N = 465	N = 186	N = 127
Age Adjusted Rate (95% CI)	138 (132,144)	114 (108, 120)	116 (110, 122)	95 (90, 101)	40 (36, 43)	34 (31, 37)	14 (12, 16)	9 (8, 11)
Age Specific Rates								
<65 yr	71	58	59	49	20	17	9	6
65-74 yr	411	336	334	268	130	112	45	26
75-84 yr	662	538	564	459	193	157	41	41
≥ 85 yr	900	781	781	674	237	222	61	23

VTE = venous thromboembolism
DVT = deep vein thrombosis
PE = pulmonary embolism
* All rates are per 100,000 population

Table 2
Clinical Characteristics of Patients with Venous Thromboembolism and Utilization of Diagnostic and Therapeutic Modalities According to Age

	< 65 years (n=849)	> 65 years (n= 1048)	P-value	< 65 years (n=849)	65-74 yrs. (n=354)	75-84 yrs. (n=463)	≥85 years (n=231)	P -value for trend
Demographic Characteristics								
Age, mean (years)	47.6	78.0		47.6	69.8	79.3	87.8	
Female (%)	48.1	60.8	<0.001	48.1	53.8	60.8	71.8	<0.001
Medical Characteristics (%)								
* Recent Prior Hospitalization	31.6	44.9	<0.001	31.6	42.9	48.2	41.1	<0.001
Recent Surgery	29.1	26.5	0.35	29.1	32.2	27.0	15.6	<0.001
Recent Malignancy	20.7	37.3	<0.001	20.7	43.5	36.3	29.8	<0.001
Recent Severe Infection*	23.3	28.2	0.017	23.3	22.0	30.5	32.9	<0.001
Admission with non-VTE related diagnosis (immediately prior event)	23.7	31.7	<0.001	23.7	29.1	33.9	31.2	<0.001
Recent Central Venous Catheter	20.6	16.6	0.025	20.6	18.1	17.9	11.7	0.005
Prior VTE	17.4	17.4	0.97	17.4	18.1	18.8	13.4	0.50
Recent ICU Discharge	15.2	17.5	0.18	15.2	19.5	18.6	12.1	0.98
Recent Intubation	15.7	15.8	0.92	15.7	20.3	15.8	9.1	0.08
Recent Hormonal Therapy	7.4	6.5	0.69	7.4	10.7	5.2	3.9	0.03
Recent Fracture	10.1	10.8	0.42	10.1	8.2	11.9	15.6	0.03
Recent Chemotherapy	8.4	7.6	0.76	8.4	11.6	8.2	2.6	0.04
Recent Heart Failure	4.5	9.9	<0.001	4.5	8.2	12.1	13.0	<0.001
Recent Cardiac Procedures	2.6	5.6	<0.001	2.6	7.1	6.7	1.7	0.15
Other medical history (%)								
Prior IVC filter	7.7	8.3	0.007	7.7	7.6	7.8	10.4	0.0006
Prior CVA	6.1	16.9	<0.001	6.1	10.7	19.9	20.4	<0.001
Diabetes	14.7	23.1	<0.001	14.7	26.0	24.0	16.9	0.008

	< 65 years (n=849)	> 65 years (n= 1048)	P-value	< 65 years (n=849)	65-74 yrs (n=354)	75-84 yrs. (n=463)	≥85 years (n=231)	P -value for trend
Hypertension	33.5	68.4	<0.001	33.5	67.2	70.0	67.1	<0.001
Ischemic heart disease	9.8	30.7	<0.001	9.8	29.7	33.7	26.4	<0.001
Inflammatory bowel disease	1.4	2.8	0.04	1.4	3.7	2.4	2.2	0.284
Liver disease	1.8	0.5	0.006	1.8	0.6	0.4	0.4	0.015
Chronic renal insufficiency	3.8	8.5	0.005	3.8	7.3	9.7	7.7	0.011
Dialysis dependent	2.1	2.4	0.70	2.1	4.0	1.5	1.7	0.50
VTE Type								
Hospital Acquired	22.6	29.1	0.002	22.6	26.3	30.7	29.9	0.001
Community Acquired*	77.4	70.9		77.4	73.7	69.3	70.1	
Unprovoked*	29.7	18.0	<0.001	29.7	17.8	16.6	20.8	<0.001
Provoked*	49.6	44.7		49.6	38.7	47.1	49.4	
Malignancy-related	20.7	37.3		20.7	43.5	36.3	29.9	

* Definitions

Recent - occurring or active in the 3 months prior to index DVT or PE

Severe infection = infections were limited to those involving the blood, bone and joint, central nervous system, cardiovascular system, gastrointestinal system, respiratory system (pneumonia only), surgical sites, or the skin.

Unprovoked VTE = Any VTE in which there is NO recent fracture, recent trauma, recent surgery, recent hospitalization, current hospitalization, central venous catheter, pregnancy, hormonal therapy, or malignancy

Provoked VTE = Total VTE - unprovoked-malignancy

Community acquired = VTE not occurring during hospitalization and diagnosed within 48 hours of hospital encounter

Table 3
Early Treatment of Patients with Venous Thromboembolism According to Age

	< 65 years (n=849)	> 65 years (n= 1048)	P-value	< 65 years (n=849)	65-74 yrs (n=354)	75-84 yrs. (n=463)	≥85 years (n=231)	P -value for trend
Acute treatment								
UFH alone	37.2	38.7	0.003	37.2	40.7	38.2	36.8	0.36
LMWH alone	30.7	30.3		30.7	31.1	29.4	30.7	
Both	17.1	11.8		17.1	11.3	11.7	13.0	
None of the above	15.0	19.2		15.0	17.0	20.7	19.5	
Other parenteral anticoagulant	2.0	1.9	0.89	2.0	1.4	2.4	1.7	0.93
Warfarin	77.4	69.0	<0.001	77.4	74.3	67.6	63.6	<0.001
IVC filter implanted	8.5	12.8	0.007	8.5	11.6	12.7	14.7	<0.001

UFH = unfractionated heparin

LMWH = low-molecular weight heparins (enoxaparin and dalteparin)

IVC = inferior vena cava

Table 4

Rates of Clinical Outcomes of Patients with Venous Thromboembolism According to Age

	< 65 years (n=849)	≥65 years (n=1048)	P-value
30-day outcomes (%)			
Major Bleeding	4.8	9.2	<0.001
Recurrent VTE (DVT or PE)	5.6	3.9	0.30
Recurrent PE (with or without DVT)	1.6	1.0	0.50
Mortality	4.2	11.2	<0.0001
1-year outcomes (%)			
Major Bleeding	6.8	13.6	<0.001
Recurrent VTE (DVT or PE)	14.0	10.8	0.30
Recurrent PE (with or without DVT)	4.1	2.7	0.50
Mortality	13.8	30.9	<0.001
3-year outcomes (%)			
Major Bleeding	8.8	16.9	<0.001
Recurrent VTE (DVT or PE)	18.3	17.0	0.30
Recurrent PE (with or without DVT)	5.0	4.9	0.50
Mortality	18.3	44.6	<0.001

Table 5
Predictors of Recurrent VTE, Major Bleeding, and Death over 3-Year Follow-up

	Recurrent VTE	Major Bleeding	Death
Demographic	Hazards Ratio (95% CI)	Hazards Ratio (95% CI)	Hazards Ratio (95% CI)
Age >65 years	0.58 (0.38, 0.90)	1.71 (1.05, 2.76)	2.31 (1.60, 3.34)
Female	1.09 (0.75, 1.60)	1.23 (0.79, 1.90)	1.00 (0.73, 1.37)
Recent** Medical History			
Recent** hospitalization	0.95 (0.61, 1.47)	1.41 (0.86, 2.30)	0.80 (0.57, 1.10)
Active malignancy	0.99 (0.44, 2.25)	3.34 (1.22, 9.19)	1.77 (0.83, 3.77)
Recent severe infection	0.97 (0.59, 1.61)	0.96 (0.56, 1.63)	1.59 (1.12, 2.27)
Hospitalization for non-VTE condition prior to VTE	1.33 (0.62, 2.83)	1.63 (0.73, 3.63)	1.79 (1.05, 3.06)
Recent central venous catheter	1.05 (0.57, 1.92)	1.19 (0.61, 2.30)	1.41 (0.90, 2.21)
Recent ICU discharge	0.68 (0.34, 1.36)	1.48 (0.77, 2.86)	0.56 (0.35, 0.91)
Recent heart failure	1.29 (0.60, 2.78)	0.48 (0.19, 1.21)	2.26 (1.45, 3.51)
Recent cardiac procedure	1.47 (0.55, 3.98)	0.52 (0.15, 1.84)	0.61 (0.27, 1.37)
Prior IVC filter	1.95 (0.99, 3.83)	1.78 (0.76, 4.20)	0.96 (0.49, 1.88)
Other Medical History			
Prior cerebrovascular event	0.50 (0.28, 0.89)	0.96 (0.50, 1.83)	0.67 (0.45, 1.01)
Diabetes	1.18 (0.69, 2.01)	0.71 (0.42, 1.19)	0.80 (0.56, 1.15)
Hypertension	0.97 (0.64, 1.49)	1.01 (0.63, 1.64)	1.31 (0.93, 1.86)
Ischemic heart disease	0.65 (0.37, 1.17)	1.13 (0.66, 1.94)	1.07 (0.74, 1.56)
Inflammatory bowel disease	0.53 (0.19, 1.47)	0.60 (0.21, 1.73)	0.63 (0.28, 1.41)
Liver disease	1.72 (0.23, 12.88)	0.41 (0.09, 1.83)	0.55 (0.19, 1.57)
Chronic renal insufficiency	0.84 (0.38, 1.85)	0.65 (0.29, 1.43)	0.93 (0.54, 1.62)
VTE Type			
Community Acquired	1.24 (0.57, 2.69)	0.97 (0.44, 2.13)	1.35 (0.80, 2.30)
Unprovoked	1.29 (0.75, 2.22)	0.61 (0.30, 1.23)	1.45 (0.82, 2.57)
Deep vein thrombosis	0.78 (0.49, 1.26)	1.59 (0.98, 2.59)	1.26 (0.88, 1.80)
Acute Treatment			
Unfractionated heparin	0.75 (0.47, 1.19)	1.65 (0.99, 2.75)	1.12 (0.77, 1.63)
Low-molecular-weight heparin	0.67 (0.43, 1.04)	1.85 (1.11, 3.07)	0.73 (0.51, 1.05)
Warfarin	0.99 (0.60, 1.63)	0.69 (0.40, 1.17)	0.53 (0.37, 0.76)
No anticoagulant treatment	1.033 (0.46, 2.35)	0.77 (0.25, 2.36)	1.00 (0.53, 1.89)
Complications			
Major bleed during follow-up	3.18 (1.83, 5.54)	- -	1.97 (1.36, 2.86)
Recurrent VTE during follow-up	- -	3.90 (1.94, 7.84)	1.08 (0.73, 1.58)