Original article

Characteristics and Outcomes of Patients With Deep Vein Thrombosis Diagnosed in Emergency Department of Clinical Hospital Dubrava During 2019

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Abstract

Aim: Deep vein thrombosis (DVT) is a common clinical condition encountered in the emergency department (ED). The aim of this study was to compare the characteristics and outcomes of patients with respect to treatment using novel oral anticoagulants (NOAC).

Materials and Methods: In this retrospective observational study, we analyzed medical records of patients diagnosed with DVT during 2019 in the ED of the Clinical Hospital Dubrava. We identified 295 patients, who comprised 1.2% of all patients examined in the ED.

Results: Women were more frequently diagnosed with DVT (59%) and they were older than the men (median age 69 vs. 62 years, respectively). Patients with proximal deep vein thrombosis (71%) were admitted to the hospital. Two thirds of all patients were treated with NOAC. Rivaroxaban was the most commonly prescribed drug (52% of patients). Control Doppler ultrasound was performed in 58% of the patients, and complete resolution was observed in 63% of the cases. NOACs caused significantly fewer bleeding events than warfarin (3.2% vs. 13.6%, $p < 0.05$).

Conclusion: Our results demonstrate that patients with DVT can be safely treated with NOACs in an outpatient setting.

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Introduction

Deep vein thrombosis (DVT) is a clinical condition diagnosed in the emergency department (ED) on a daily basis. The average annual incidence rate of venous thromboembolism (VTE) in Europeans ranges from 1.04 to 1.83 per 1,000 person-years (1). Separately, pulmonary embolism (PE) with or without DVT varies from 0.29 to 0.78 per 1,000 person-years. DVT incidence rate ranges from 0.45 to 1.17 per 1,000 person-years. The total age-adjusted incidence rate is higher for men (1.3 per 1,000 person-years) than women (1.1 per 1,000 person-years) (1). The incidence rate in the population younger than 45 is 0.12 per 1,000 person-years, and 2.62 per 1,000 person-years in the population older than 65(2). In fact, DVT primarily affects older people.

DVT occurs as a result of three overlapping mechanisms, known as Virchow's triad: venous stasis, endothelial injury and hypercoagulability. The most important one is venous stasis, but it is not sufficient for thrombus formation in and of itself. Venous valve pockets are places of reduced blood flow in which thrombi develop. As a result of the blood flow slowing down, partial pressure of oxygen declines and consequently leads to local hematocrit increase. Higher expression of prothrombotic and lower expression of antithrombotic proteins further enhance the hypercoagulable microenvironment. Intact endothelial surface has antithrombotic and anticoagulant characteristics. Endothelial dysfunction or injury promotes contact of venous blood with tissue factor and thrombin, which activates the coagulation cascade (3, 4).

In Croatia, according to the study conducted by the Croatian Cooperative Group for Hematologic Diseases (KROHEM) in 2011, the estimated annual incidence of VTE was 1.185 per 1,000 people (5). The incidence of DVT was 0.79 per 1,000 people, with female predominance (56.3%). There were more patients with secondary VTE (57.3%), and malignant disease was the most frequent cause.

Since 2011, novel oral anticoagulants (NOAC) have emerged as a novel treatment option, in addition to low-molecular-weight heparin (LMWH) and vitamin K antagonists (VKAs). Three NOACs were available in Croatia in 2019, however, only with partial reimbursement by national insurance: dabigatran (prothrombin inhibitor), rivaroxaban and apixaban (factor Xa inhibitors). Other than venous thromboembolism, indications for NOACs are atrial fibrillation and prevention of thromboembolic complications after a stroke or myocardial infarction. Their use is simpler, with fixed oral dosing, there is no need for laboratory monitoring and they do not depend on the diet. Patients can be treated with rivaroxaban and apixaban without LMWH as the standard initial therapy for DVT. Apixaban and dabigatran require dosing twice per day, as opposed to rivaroxaban, which requires use once per day (6).

The aim of this study is to determine the clinical characteristics, treatments and outcomes of patients who were diagnosed in the ED of the Clinical Hospital during 2019.

Patients and Methods

Study design

This study was designed as a retrospective analysis of electronic hospital charts of patients diagnosed with DVT in the Emergency Department of the Clinical Hospital Dubrava, Zagreb, Croatia, during 2019.

Patients and definitions

A total of 399 patients with VTE were diagnosed from 1 January to 31 December 2019. Patients that presented with PE without proven DVT were not included. Medical records of the remaining 295 patients with DVT were analyzed. Diagnosis was established based on clinical examination, D-dimer test and Doppler ultrasound. The following data were collected: age, sex, date of diagnosis, thrombosis type (proximal or isolated distal deep vein thrombosis; or other thrombosis), admission to hospital, treatment, idiopathic or secondary DVT. DVT was

considered secondary if some of the following risk factors were identified: malignant disease within 6 months of the event; recent trauma, surgery, immobilization/immobility; use of oral contraceptives; pregnancy; inflammatory bowel disease and thrombophilia. DVT was considered idiopathic if none of above factors were present. In our study, bleeding was considered significant if a patient required examination in the emergency department.

Statistical analysis

Categorical data are presented with absolute (N) and relative frequencies and compared using the $\chi 2$ test or Fisher's exact test, where applicable. Numerical data are presented with median and range values and compared using the Mann-Whitney U test. The probability value of < 0.05 was considered statistically significant. Estimated annual incidence per 1,000 inhabitants was calculated using the number of recorded new DVT cases divided by the population which gravitates to this hospital. Microsoft Excel was used for statistical analysis.

Ethics

Our research was conducted in full compliance with the Declaration of Helsinki and it was approved by the Ethics Committee of the Clinical Hospital Dubrava.

Results

A total of 295 patients were diagnosed with DVT, and 104 were diagnosed with PE (without concomitant DVT) out of a total of 23,899 patients examined in the ED in 2019 (Figure 1).

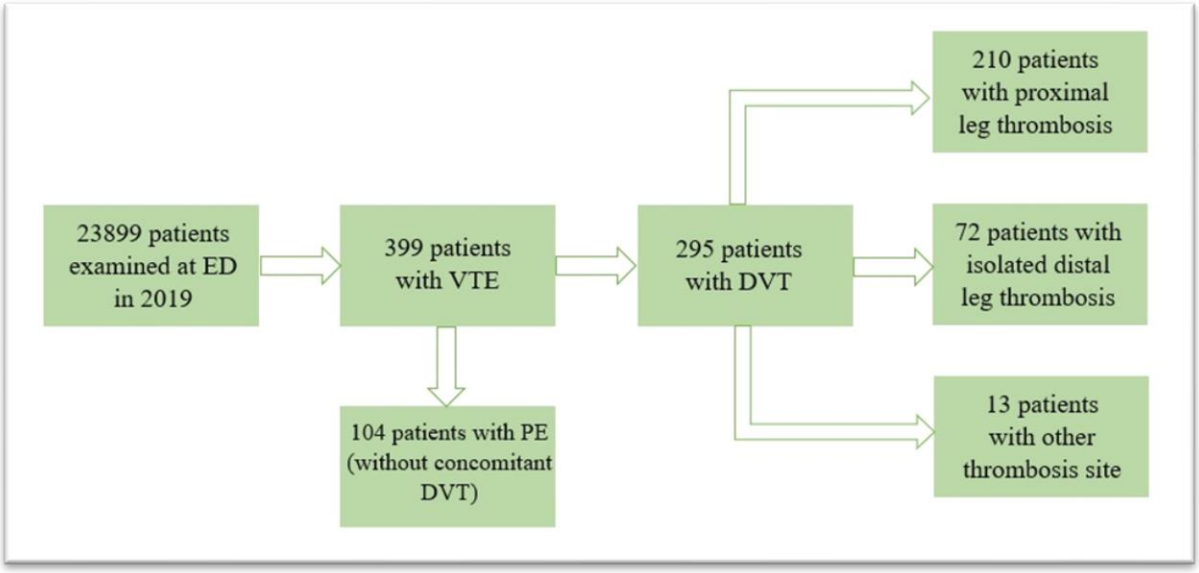

Figure 1. Patient flowchart (total N = 23,899)

ED = emergency department, VTE = venous thromboembolism, PE = pulmonary embolism, DVT = deep vein thrombosis

It should be noted that 55 DVT patients (13.8% of the total number) were diagnosed with concomitant PE. Thus, DVT frequency in our ED was 1.23% and PE frequency was 0.67%. Total VTE frequency was 1.67%. Considering the number of people gravitating to the Clinical Hospital Dubrava (which is about 330,000), the estimated annual DVT incidence was 0.894 per 1,000 people.

Median age was 65 years, ranging from 20 to 94 years. Women comprised 59% of patients (174 out of 295). Women were older (median 69 years; range 22 to 90) than men (median 62 years; range 20 to 94) ($p = 0.005$). However, in the younger age groups, the incidence of thrombosis was higher in men (Figure 2)..

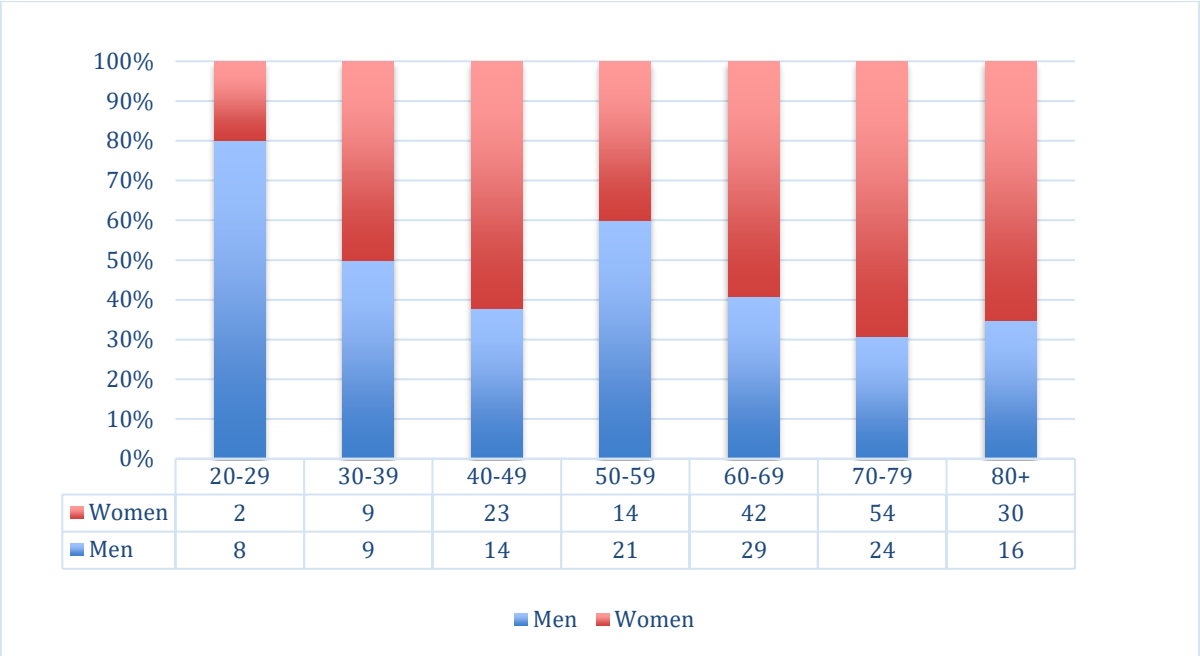

Figure 2. Proportion of men and women with deep vein thrombosis according to age groups (total N = 295)

Admission to the hospital was required for 206 patients (69.8%), and 73 patients (24.8%) were treated in an outpatient setting, while 16 (5.4%) refused hospitalization or were sent to another hospital. The patients who were admitted to the hospital were older compared to those who were discharged from the ED (median age was 69 years (range 20 to 94) vs. 60 years (range 25 to 88), respectively) (p = 0.0002).

Proximal DVT (thrombosis of the popliteal vein and of the femoral veins) was diagnosed in 210 patients (71.2%), while isolated distal DVT was diagnosed in 72 patients (24.4%) (Figure 1). Of the 13 patients with other thrombosis, IVC thrombosis was diagnosed in four patients (1.4%), internal jugular vein thrombosis in two patients (0.6%) and thrombosis of arm veins in seven patients (2.4%). Of the patients with leg thrombosis, left leg thrombosis occurred in 51.8% of patients compared to 46.5% of patients with right leg thrombosis (1.7% had thrombosis in both legs). A total of 67 patients (22.7%) had recurrent DVT. Divided by gender, there were 37 women (21.3%) and 30 men (24.8%) with recurrent DVT (p = 0.38).

Table 1. Secondary DVT* causes (total N = 170)

DVT CAUSES	N (%)
MALIGNANT DISEASE	69 (40.6%)
TRAUMA, OPERATION, IMMOBILIZATION	56 (32.9%)
IMMOBILITY	19 (11.2%)
HORMONAL CONTRACEPTION	4 (2.4%)
OTHER	22 (12.9%)

**DVT = deep vein thrombosis*

A provoking factor was identified in 170 patients (57.6%), while 125 patients (42.4%) did not have any factors in their medical documentation. Patients with idiopathic DVT appear to be older (median age 67 years) than those with secondary thrombosis (median age 64 years) (p

= 0.435). The most common provoking factor in the group of secondary DVT patients was active malignant disease in 69 patients (40.6%) (Table 1). Based on gender, there were 38 women (37.6%) and 31 men (44.9%) with malignant disease as a provoking factor (p = 0.34). Recent trauma, surgical procedure or limb immobilization was present in 56 patients (32.9%). There were 19 immobile patients (11.2%), while four patients (2.4%) were using oral contraceptives. The remaining 22 patients (12.9%) with secondary DVT had inflammatory bowel disease, thrombophilia, were pregnant, or failed to adhere to anticoagulant treatment after previous VTE.

Initial treatment with LMWH was started in 264 patients (90.7%). The most frequent treatment after initial LMWH was rivaroxaban in 130 patients (44.1%) (Table 2). Rivaroxaban without previous LMWH therapy was used in 24 patients (8.1%). The second most frequent therapeutic option was warfarin after LMWH, in 59 patients (20%). Long-term LMWH therapy was the option of choice for 46 patients (15.6%), mainly for patients with active malignant disease. Dabigatran or apixaban after initial LMWH treatment was used in 31 patients (10.5%). Acenocoumarol was the treatment option for one patient (0.3%). Therapy for four patients (1.4%) is unknown due to their transfer to another hospital.

Table 2. Treatment modalities (total N = 295)

THERAPY	N (%)
RIVAROXABAN AFTER STARTING LMWH*	130 (44.1%)
RIVAROXABAN WITHOUT PREVIOUS LMWH	24 (8.1%)
WARFARIN	59 (20%)
LONG-TERM LMWH	46 (15.6%)
DABIGATRAN/APIXABAN	31 (10.5%)
ACENOCOUMAROL	1 (0.3%)
UNKNOWN	4 (1.4%)

**LMWH = low-molecular-weight heparin*

We also compared the bleeding in patients on NOAC and warfarin. Of the 185 patients treated with NOAC, there were only six significant bleeding events (3.2%) that required medical attention in the ED. In comparison, of the 59 patients treated with warfarin, eight bleeding events were documented (13.6%). This is a statistically significant difference; p = 0.0067.

The median follow-up period for all patients was 260 days (range 3 to 648 days), with 45 (15.3%) patients lost to follow-up. Patients treated with warfarin had a similar median follow-up period compared to those treated with NOAC, 237 days (range 6 to 613 days) and 280 days (range 3 to 648 days), respectively. A follow-up Doppler ultrasound was performed in 170 patients (57.6%); 116 patients (39.3%) did not come for a follow-up examination in our institution, 6 (2.1%) were treated in another hospital and 3 patients (1%) died during or soon after hospitalization. Complete resolution was confirmed in 107 patients (62.9%), partial resolution was found in 60 patients (35.3%), and 3 patients (1.8%) did not show any improvement. Of the 129 patients treated with NOAC with available follow-up, 80 patients showed complete resolution (62%), whereas of the 31 patients treated with warfarin, 17 patients showed complete resolution (55%); p = 0.10.

Discussion

This study provided a valuable insight into the clinical characteristics and treatment of patients with DVT in Croatia in the era of NOACs. Estimated annual incidence of VTE from this research is consistent with other published studies (1, 2, 5). VTE frequency in the ED of the Clinical Hospital Dubrava is comparable to the

study conducted by KROHEM, and is almost identical to the Spanish study (1.67% vs. 1.65%) (7).

An interesting finding of this study is that DVT was diagnosed more frequently in women. In this study, we had 59% of women with DVT, which is comparable to other studies (JAVA, KROHEM) (5, 8). According to the estimation by the Croatian Bureau of Statistics, the proportion of women in the general population in 2018 was 51.7%, with increasing numbers in older age groups, and the average life expectancy of women in Croatia is 7 years longer than that of men (10). However, in patients younger than 65, there were only 48.6% of women (Figure 2). Overall, it seems that the female sex is not an independent risk factor for DVT.

Interestingly, there was a higher rate of simultaneous DVT and PE (13.8%) than in the study conducted by KROHEM (5.4%), while the Japan VTE Treatment Registry (JAVA) reported a rate of 14.4% (8). A reason for such difference could be the more frequent use of pulmonary angiography compared to the general hospitals included in the KROHEM study eight years prior to this study. It is known that with proximal DVT, asymptomatic pulmonary embolism can occur in 35% of the cases (9). Conversely, in patients with PE, deep vein thrombosis can be diagnosed in up to 71% of all patients (10). It is important to note that the ratio between proximal and distal DVT in our study is comparable to other studies, such as the Norwegian study, which reported 69.6% of patients with proximal DVT and 27.2% of patients with distal DVT (2).

Almost two thirds of the patients in 2019 were treated with NOACs, and one quarter of the patients were treated in an outpatient setting. Also, a substantial finding of this study is that NOACs cause fewer bleeding events compared to warfarin. Introducing NOACs into everyday clinical practice enabled a higher rate of outpatient management. For instance, in a Spanish study conducted in 2002, 99% of patients with PE and 85% of patients with DVT were admitted to the hospital (12). A more recent study from Spain, conducted in 2014 in 53 EDs across Spain, reported that 98.7% of patients with PE and 50.2% of patients with DVT were hospitalized (7). In our study, 71% of the patients were admitted to the hospital. This fully corresponds to the proportion of patients with proximal DVT. In other words, patients with distal DVT were treated in an outpatient setting using NOACs.

The prevalence of DVT on the left side (52.7% vs. 47.3%) found in our study was also observed in other studies (13, 14). The only valid explanation for that difference is compression of the left common iliac vein by the right common iliac artery (May-Thurner syndrome) (13). The proportion of idiopathic venous thrombosis in our cohort (42.4%) is consistent with other studies. Idiopathic thrombosis was diagnosed in 43.2% and 42.7% of the patients in the JAVA and the KROHEM studies, respectively (5, 8). Both the KROHEM study and this study report on the greater age of patients with idiopathic thrombosis compared to patients with secondary thrombosis. Venous thromboembolism is a well-known complication of malignant disease. In a recent study conducted on 1,041 patients with solid tumors, 7.8% of patients had a thromboembolic event (15). Both the KROHEM study and this study recognized malignant disease as the leading cause of secondary thrombosis. The second most common cause (trauma, surgical procedure and immobilization) was less frequent in this study (32.9%) compared to the KROHEM study (38.2%). Inability to move as a result of paralysis or frailty is considered to be the third most common risk factor. Oral hormonal contraception (OHC) is an important risk factor in the population of fertile women (15–45 years). Of the 16 fertile women with secondary thrombosis, 4 had OHC in their medical history (25%). The RIETE study reported that 36% of women with VTE younger than 50 years were using OHC (16). Other risk factors were less frequent (Table 1).

Initial treatment with LMWH was used in 94% of patients included in the Spanish study (7). That percentage is comparable to this study (90.7%). There were 12,585 patients with the first VTE episode included in a large Norwegian study, which excluded patients with malignant disease (17). Rivaroxaban was a treatment option in 46.3%

of patients, warfarin in 28.3%, apixaban in 24.5% and dabigatran in 0.7%. This study included patients with malignant disease, of whom two thirds were treated using prolonged LMWH therapy. Considering the entire DVT population, the most commonly used therapeutical option was rivaroxaban (52.2%) (Table 2). It is known that outpatient management using rivaroxaban can be efficiently performed in low-risk patients, with a low rate of bleeding and recurrent thrombotic events (18).

Other NOACs were less commonly prescribed (10.5%). This may be explained by the fact that dabigatran requires five days of prior LMWH treatment, which is complicated in an outpatient setting, as well as by the fact that apixaban was introduced in Croatia several years after rivaroxaban. On the other hand, warfarin was prescribed to 1 in 5 patients (Table 2). It is obvious that NOACs are the preferred choice for an increasing number of patients. In addition, patients report greater satisfaction with NOACs compared to warfarin (19). One of the reasons for that is the lower incidence of bleeding when using NOACs (20), which was confirmed in this study. We observed statistically fewer serious bleeding events in patients treated with NOACs compared to those treated with warfarin (Table 3).

Table 3. Bleeding during treatment with NOAC* and warfarin (total N = 244)

	N	Bleeding	Incidence
Warfarin	59	8	13.6%
NOAC	185	6	3.2%

**NOAC = novel oral anticoagulants*

Deep vein thrombosis is a disease which requires regular check-ups because of the high incidence of recurrent thrombosis. The five-year cumulative incidence of recurrent VTE events is 21.5% after the first DVT episode and 27.9% after the second (21). We had 22.7% patients with recurrent DVT after previous VTE. As a comparison, in the study conducted by KROHEM, recurrent VTE was diagnosed in only 11.9% of patients (5). However, as many as 39% of the patients diagnosed with DVT in our cohort in 2019 have had no further ultrasonographic check-ups in our institution. This could be explained by the fact that Clinical Hospital Dubrava was the national COVID-19 hospital during a few months in 2020 and 2021 and the patients were probably followed-up on in other institutions. Data about check-ups (and complications) observed in other institutions are not available. That is the main weakness of our study. Nevertheless, complete DVT resolution was documented in almost two thirds of our patients. There was a trend toward better efficacy of NOAC compared to warfarin; however, it did not reach statistical significance.

Despite the limitations of a retrospective study, we believe that our center's experience from 2019 shows the general characteristics of patients with DVT in Croatia. The incidence and characteristics of patients are comparable to those observed in the study conducted by KROHEM.5 However, the introduction of NOACs in the last few years has facilitated the outpatient treatment of such patients, at least those with distal thrombosis. We believe that even more patients will be treated with NOACs in the future.

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Competing interests. None to declare

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