LOW RATE OF INTRA-HOSPITAL DEEP VENOUS THROMBOSIS IN ACUTELY ILL MEDICAL PATIENTS. Results from the AURELIO study.

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Abstract:

Background: Guidelines recommend prophylactic doses of parenteral anticoagulants in acutely ill medical patients to prevent deep venous thrombosis (DVT) during the hospital stay. However, it has not been clarified if DVT is already detectable at admission. This study sought to evaluate the effect of hospitalization on DVT rate by the cumulative incidence of DVT in the proximal venous tract of the lower limbs at admission and discharge.

Methods: Multicenter observational study was underwent in hospital-university internal medicine wards including consecutive acutely ill medical patients. Patients underwent compression ultrasonography (CUS) of proximal lower limb veins at admission and discharge. DVT occurrence was the primary end-points of the study.

Results: Among 1,340 patients, 26 (1.9%) had asymptomatic DVT at admission and were excluded. During the follow-up, 144 patients were excluded because of hospitalization less than 5 days. The remaining 1,170 patients underwent a CUS at discharge. Two-hundred and fifty (21%) underwent a prophylaxis with parenteral anticoagulants; the remaining 920 (79%) were not treated with anticoagulants. The mean length of hospitalization was 13±8 days. Compared to patients without prophylaxis, those treated with parenteral anticoagulants had higher incidence of active cancer, heart and respiratory failure, pneumonia, renal failure, previous VTE, reduced mobility and elderly age. During the hospital stay, three patients with a negative CUS at admission, experienced DVT in the proximal tract (0.025%, rate of 1 per 5017 patient-days); two of them were in prophylaxis with parenteral anticoagulants.

Conclusions: We provide evidence that in the real world acutely ill medical patients display 1.9% (1.3%-2.8%) asymptomatic DVT at admission while the intra-hospital DVT occurrence is very low. This suggests a novel diagnostic work-up and a careful re-analysis of anticoagulant prophylaxis.

Keywords: deep venous thrombosis, medical patients, compression ultrasonography, anticoagulants.

Introduction

Hospitalization for acutely ill medical patients is associated with an approximate eight-fold increased risk of developing venous thromboembolism[1]. For this reason, guidelines from the American College of Chest Physicians recommend to prescribe in-hospital thromboprophylaxis to reduce the incidence of deep venous thrombosis (DVT) in acutely ill medical patients[2].

Prospective studies in selected population showed that asymptomatic DVT occurs on average 4.4% of patients while the rate of symptomatic DVT is much less (0.75%)[3]. However, a lower incidence of intra-hospital DVT (0.3-0.5%) has been reported in two registry studies, the REPOSI and Improve Studies, including unselected population[4, 5].

Based on this assumption several randomized clinical trials (RCT) with anticoagulants, including low-molecular-weight heparin (LMWH), fondaparinux and more recently direct oral anticoagulants (DOAC), showed that prophylaxis with anticoagulants reduces the risk of composite endpoints of DVT, pulmonary embolism (PE) and DVT-related death[3]. These results prompted recommendations for the use of anticoagulant prophylaxis in patients hospitalized for acute medical illness and scores to identify patients at risk of DVT[2, 5]. For instance, a recent study in a large population demonstrated that previous DVT, cancer, age>60 or immobilization may identify patients at risk of DVT[5]. Furthermore, the Padua score included clinical settings potentially enhancing the risk of DVT such as active cancer, previous venous thrombo-embolism (VTE), reduced mobility, already known thrombophilia condition, recent trauma and/or surgery, elderly age>70 years, heart and/or respiratory failure, acute myocardial infarction or ischemic stroke, acute infection and/or rheumatologic disorder, obesity with BMI>30 and ongoing hormonal treatment[6]. However, their predictive value needs to be confirmed in large prospective studies[6]. More recently, Cohen et al suggested that patients older than 75 with positive D-dimer could be at higher risk of DVT[7]. Thus, an important issue is to establish if specific clinical settings carry a risk of DVT in acutely ill medical

patients and the impact of hospitalization on the DVT risk. In this context it is worth mentioning that previous observational and clinical trials have used a doppler ultrasonography assessment at approximately 10 days after admission, which did not exclude that DVT could be already present (and detectable) at admission[8]. Addressing this issue might have relevant clinical implications, not only for an early DVT diagnosis, but also for optimizing the therapeutic strategy.

On this basis, the main objective of the study was to evaluate the rate of DVT in hospitalized acutely ill medical patients by analyzing the presence of DVT by CUS underwent at patient admission and discharge. For this purpose we performed a multicenter prospective study in >1000 acutely ill medical patients consecutively admitted to internal medical wards. Here we provide the first evidence that in this clinical setting the majority of asymptomatic DVT is already detectable at admission while the intra-hospital DVT rate is low.

Material and Methods

One thousand three hundred and forty consecutive non-selected patients with acute medical conditions of any kind requiring hospitalization in the internal medicine departments of the participating centers were recruited from February 2015 to July 2017. Ten centers associated to the ultrasound Study Group of the Italian Society of Internal Medicine participated in this study. A detailed clinical history was collected at admission.

To be enrolled medical patients had to be hospitalized at least 5 days. Reasons for exclusion were treatment with anticoagulant therapy at admission, surgical procedures 4 weeks before or 2 weeks after admission to the medicine ward, treatment with vitamin k inhibitors, acute symptomatic DVT and acute PE, patients admitted in internal medicine wards from the intensive care units or patients without CUS at discharge. Each center was advised to follow the local standard therapeutic management of acutely ill medical patients.

Reduced mobility was defined as requiring total bed rest or being sedentary with bathroom privileges for at least 3 days. Clinical conditions and comorbidities were recorded on the basis of

patient documentations or medical history. During the hospitalization study: heart failure was defined according to the 2013 ACCF/AHA Guideline for the Management of Heart Failure[9]; syncope, myocardial infarction and stroke were defined as previously reported[10-12]; respiratory failure was defined as a syndrome in which the respiratory system fails with hypoxemic or hypercapnic conditions; sepsis was defined according to the definition of ACCP[13], COPD was defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[14].

Ultrasonography was underwent and interpreted by internists with adequate experience with color Doppler ultrasonography. Ultrasonography was routinely used to verify the diagnosis of venous thrombosis in all participating centers; no specific training for the study was requested because all the internists that executed CUS participated to the ultrasound training program of the Italian Internal Medicine Society (SIMI). At least 2 internist per unit performed CUS; a second internist had to perform a confirmatory CUS after DVT identification. Internists were selected within the Italian Internal Medicine Society (SIMI) Ultrasound Study Group[15].

The index test was a CUS underwent by participating MDs with a ultrasound machine equipped with 7.5–10 MHz linear-array transducer. For obese subjects, a 3.5 MHz curvilinear transducer was available. Color Doppler imaging assisted vessel identification.

CUS was executed within 48 hours from the admission at the hospital. CUS was underwent with a standardized protocol as previously described[16]. After identification of the common femoral artery and vein located just inferior to inguinal ligament, pressure was applied until common femoral vein was completely compressed; superficial femoral vein and popliteal vein were identified and examined as a common femoral vein. Visualization of intraluminal thrombosis or incomplete compressibility of any target vein, despite adequate pressure, rendered an examination positive[16]. Examinations demonstrating complete compressibility of all target veins were considered negative[16]. CUS was underwent at admission and discharge in all patients.

The primary outcome was the incidence of DVT in the proximal venous tract of the lower limbs at admission and discharge.

All procedures underwent in this study were in accordance to the ethical guidelines of the 1975 Declaration of Helsinki; the study was approved by the Ethical Committee of participating centers and was registered on ClinicalTrials.gov (Identifier: NCT03157843).

Statistical analysis

Continuous variables are reported as mean ± SD and categorical variables are reported as n (%). The association between continuous variables across categories was assessed using a Mann Whitney test, since the assumption of normality was not tenable. The association between categorical variables was assessed using a Chi square test. Intra-hospital DVT, being a rare event, was modeled according to a Poisson distribution. $P<0.05$ was considered as statistically significant. All analyses were carried out with SPSS V.18.0 (SPSS Statistics v. 18.0, SPSS Inc. Chicago, USA).

SAMPLE SIZE calculation

The main endpoint concerns the incidence of DVT evaluated by CUS. Previous retrospective studies showed an incidence of 4.4%; assuming this incidence as maximal, we calculated that 1,336 patients would guarantee a total confidence interval length of at most 2.2%, which is half the expected incidence. Any incidence lower than 4.4% guarantees even shorter confidence intervals.

Results

At admission CUS was underwent in one thousand three hundred forty patients; five hundred patients (37%) were from northern Italian regions, 37% from the center and 25% from the southern regions; clinical characteristics of this population are reported in table 1.

Twenty-six (1.9%, 95%CI: 1.3%-2.8%) patients had asymptomatic DVT and were immediately treated with high doses of parenteral anticoagulants. Clinically characteristics of the patients hospitalized with and without asymptomatic DVT at admission are reported in table 1. During the follow-up, one hundred and forty-four patients were excluded because of hospitalization less than 5 days. CUS was underwent on the remaining 1,170 patients at discharge.

Two-hundred and fifty (21%) underwent a prophylaxis with parenteral anticoagulants; the remaining 920 (79%) did not receive prophylaxis with parenteral anticoagulants. Clinical characteristics of these two groups are reported in Table 2.

Compared to patients without prophylaxis with parenteral anticoagulants, those who received prophylaxis with parenteral anticoagulants had higher PADUA score; in particular, they showed a higher incidence of active cancer, heart and respiratory failure, pneumonia, renal failure, previous VTE, reduced mobility and elderly age (see Table 2).

The mean length of hospitalization was 13±8 days. During the hospital stay, three patients (0.25%, 95% CI 0.05%-0.75%) with a negative CUS at admission experienced DVT; with a resulting rate of 1 per 5017 patient-hospital days. Two patients showed asymptomatic and one symptomatic DVT in the proximal tract. One had heart and respiratory failure and retroperitoneal cancer, another had heart and respiratory failure and the last one sepsis. Two of them were in prophylaxis with LMWH.

The X^2 analysis showed a significant difference for age>70 (p=.03), heart failure (p<.001), respiratory failure (p<.001) and syncope (p=.02) among patients with positive vs negative CUS at admission (table 1); furthermore, a non-parametric test (Mann Whitney-U) showed a significant difference for age (p=.004) and BMI (p=.02) between the two groups (table 1). Compared to patients with negative CUS, similar findings were obtained when we included the three DVT occurred during the intra-hospital stay to the group of patients with positive CUS at admission (not shown).

Discussion

This report shows that in acutely ill medical patients almost all proximal DVT were already detectable at admission while DVT incidence during hospitalization was negligible. Also a significant association between specific clinical illness and DVT was observed.

Previous studies consistently demonstrated that acutely ill medical patients are at risk of proximal and distal DVT and that prophylactic doses of parenteral anticoagulants[3] and more recently DOAC reduce such risk[17]. In the landmark study by Samama et al[18] a selected population putatively considered at risk of DVT such as patients with heart failure, infections, acute respiratory failure, acute rheumatic disease, acute respiratory disease and inflammatory bowel disease were included and followed-up during hospital stay. In this report, as well as in other reports in which it was possible to appreciate the rate of DVT in control patients, the incidence of DVT ranged from 2.1 to 8%[8]. The present study followed a different methodological approach as we decided to include an unselected population that would allow us to appreciate the impact of DVT in the real world; furthermore, we underwent a CUS at admission and at discharge while previous reports underwent a CUS after at least one week from admission[8]. Our observational study showed that the rate of DVT is on average less than that reported in the placebo-treated patients included in previous interventional trials as approximately 2% of our patients experienced proximal DVT compared to an average 4% of previous reports[8]. A novel finding of the present study was that almost all the DVT were already detected at admission indicating that venous thrombosis was more related to the underlying clinical illness than to hospitalization per se. In fact, among the total 29 DVT, only 3 occurred during the hospitalization stay. Differently from previous studies, we did not include distal DVT as end-point. Independently from the still debated issue on the clinical impact of distal DVT on vascular outcomes[19], we decided to exclude it because diagnosis of distal DVT is cumbersome and needs specific skillful, which are hard to address in multicenter studies[19,20]. Furthermore, the rate of distal DVT, as assessed by standard diagnostic procedure, i.e. CUS, is very low in this setting with distal/proximal ration of approximately one to ten[17, 21, 22]; thus, we calculated that we could have lost no more than 2-3 cases of distal DVT, which likely impacted scarcely our global results. However, this is a study limitation which needs to be addressed in future study.

The study has implications and limitations. In this population of acutely ill medical patients the rate of DVT was approximately 2%, which is consistent with previous report including unselected population[23] but lower than that reported in selected patients[8]. However, a selection bias cannot be completely excluded in studies recruiting unselected patients (e.g. the subjects admitted to an internal medicine clinic could not represent the population at large). Additionally, we note that the accrual rate is a bit low, indicating possibly restrictive inclusion criteria. Another limitation of the study is the low sensibility and specificity of CUS to differentiate acute from chronic DVT in patients with a previous DVT[24]. The error associated with ultrasound measurements of residual vein diameter, thrombus echogenicity and flow appear to be considerable to differentiate acute from chronic phase in patients with previous DVT[24, 25]. Other limitations of the study are that the DVTs could have occurred after time of admission but before the first CUS and by the impossibility to execute the second CUS in patients who died during the hospitalization.

An important implication of the study is that most acutely ill medical patients display proximal DVT at admission and should be treated with high doses of parenteral anticoagulants or DOAC. Surprisingly, the intra-hospital rate of DVT was particularly low but we cannot exclude that other clinical illness, demographic characteristics or laboratory variables such as elevated D-dimer[26] may help to identify patients at risk of DVT, who need to be treated with prophylactic doses of anticoagulants[27]. Only 21% of patients were on treatment with prophylactic doses of LMWH, which is consistent with an underuse of anticoagulants in this setting[28]. The low rate of thromboprophylaxis of our study is consistent with a previous report by Italian Registry REPOSI (REgistro POliterapie Societa` Italiana di Medicina Interna)[4]; this registry reported that 15.2% of patients were treated with thrombo-prophylaxis in Italian internal medicine clinics[4]. Of note, patients on treatment with anticoagulants had more severe disease and experienced 2 DVT during the intra-hospital stay; we cannot exclude, however, that this DVT rate could be even higher in case of no anticoagulant treatment.

The low adherence to guidelines for DVT prophylaxis in the real world is an actual issue that could be dependent on (1) unclear relationship between DVT and acute medical diseases, (2) lack of validated scores to identify the risk to develop DVT. We should finally acknowledge that this study has been done in Italy and included essentially a Caucasian population; therefore, our data cannot be extrapolated to other ethnic groups.

In conclusion, we report that in all acutely ill medical patients most DVT are already detected at admission, suggesting the need of a novel diagnostic and therapeutic work up for DVT management. Further studies are necessary to define patients at risk of DVT during hospital stay, who need to be treated with prophylactic doses of anticoagulants.

Footnotes

Author Contributions: Prof. Violi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Legends:

Table 1: Clinical characteristics of the population and of patients with positive or negative CUS at admission. Data are reported as mean±SD for continuous variables and as patients with and without a given risk factor.

Table 2: Clinical characteristics of patients with or without parental prophylaxis.

Table 1

	Overall population	**CUS + At admission**	**CUS - At admission**	***P***
N	1340	26	1314	-
Age (years)	71±9	80±12	71±15	*.004*
Females/males	636/704	15 (57)	621 (47)	.56
Active cancer (%)	194 (14.1)	5 (19)	189 (14)	.49
Syncope (%)	45 (3.3)	3 (11)	42 (3)	*0.02*
Heart failure (%)	105 (7.8)	8 (30)	97 (7)	*<.001*
Respiratory failure (%)	74 (5.5)	9 (34)	65 (5)	*<.001*
COPD (%)	60 (4.4)	4 (15)	56 (4)	*.007*
Pneumonia (%)	128 (9.5)	3 (11)	125 (9)	.73
Sepsis (%)	35 (2.6)	2 (7)	33 (2)	.10
Renal failure (%)	268 (20)	3 (11)	265 (20)	.27
Previous VTE (%)	47 (3.5)	2 (7)	45 (3)	.24
Reduced Mobility (%)	373 (27.8)	11 (42)	362 (27)	.12
Known thrombophilia (%)	13 (1)	1 (3)	12 (1)	.13
Elderly Age (>70 years) (%)	806 (60.1)	21 (80)	785 (59)	*.03*
Recent trauma (%)	89 (12.4)	2 (8)	87 (7)	.78
Acute infections (%)	416 (31.0)	13 (50)	403 (30)	*.03*
Hormonal treatment (%)	44 (3.2)	2 (7)	42 (3)	.20
Hypertension (%)	837 (62.4)	14 (53)	823 (62)	.36
Diabetes (%)	321 (23.9)	0 (0)	321 (24)	*.004*
Current Smoking (%)	257 (19.1)	8 (30)	249 (19)	.21
Dyslipidemia (%)	399 (29.7)	4 (15)	395 (30)	.09
BMI	25.8±4.6	23.7±3.0	25.8±4.6	*.02*
Antiplatelet treatment (%)	308 (22.9)	0 (0)	308 (23)	*.005*

Table 2

	Parenteral prophylaxis	**No prophylaxis**	**P**
N	250	920	-
Age (years)	77±12	71±15	*.001*
Females/males	130/120	442/478	.18
Active cancer	50 (20)	127 (14)	.01
Syncope	10 (4)	27 (3)	*.393*
Heart failure	41 (16)	49 (5)	*<.001*
Respiratory failure	22 (9)	37 (4)	*.002*
COPD	11 (5)	40 (4)	*.97*
Pneumonia	36 (14)	78 (8)	.005
Sepsis	7 (3)	21 (2)	*.63*
Renal failure	65 (26)	172 (19)	.011
Previous VTE	17 (7)	23 (2.5)	.001
Reduced Mobility	144 (57)	189 (20)	*<.001*
Known thrombophilia	3 (1)	7 (0.7)	.50
Elderly Age (>70 years)	188 (75)	519 (56)	*<.001*
Recent trauma	24 (9)	53 (6)	*.03*
Acute infections	85 (34)	274 (29)	*.20*
Hormonal treatment	8 (3)	32 (3.5)	.83
Hypertension	165 (66)	557 (60)	.12
Diabetes	62 (25)	215 (23)	*.63*
Current Smoking	46 (18)	171 (18)	.14
Dyslipidemia	79 (31)	266 (29)	.80
BMI	25.5±4.9	25.9±4.5	*.21*
Antiplatelet treatment	38 (15)	232 (25)	<0.001
PADUA score >4	169 (67)	288 (31)	*<0.001*
Padua score	4.5±2.2	2.5±2.3	*<0.001*