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Incidence of venous thromboembolism in psychiatric units ☆

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ABSTRACT

Introduction: Incidence and risk factors of venous thromboembolism (VTE) are well established in surgical and medical settings, but data in psychiatric units are lacking. The aim of this study was to estimate the incidence of VTE in hospitalized psychiatric patients, and to assess the risk factors for VTE in this specific population.
Materials and Methods: All consecutive adult patients, admitted for a psychiatric disorder for at least seven days in psychiatric units were considered for inclusion. Patients were evaluated for signs and symptoms of VTE during hospitalization. At Day 10, all participants were interviewed and a systematic compression ultrasonography of the lower limbs was performed. Patients were followed-up until Day 90.
Results: Among the 471 included patients, 449 were evaluable at Day 10, and 458 were followed-up until Day 90. Ten deep vein thromboses (DVT) were diagnosed by Day 10 leading to an incidence of VTE of 2.2% (95% CI, 1.1%–4.1%). Six additional symptomatic VTE occurred between Day 10 and Day 90, leading to a 3.5% incidence at Day 90 (95% CI, 2.0%–5.6%). The main factors associated with VTE were age, bed rest, and diagnosis of dementia. The incidence of VTE in patients aged 75 or over with a diagnosis of dementia reached 8.2% at Day 10 and 12.5% at Day 90.
Conclusions: The incidence of VTE in psychiatric units appeared low. However, in older patients, especially those with dementia, the incidence of VTE increased considerably. Further studies are needed to confirm these results.

Introduction

Venous thromboembolism (VTE) is a common and potentially preventable cause of morbidity and mortality in hospitalized patients [1]. Risks of VTE associated with surgical procedures and medical illnesses are well established and benefit of thromboprophylaxis has been clearly demonstrated in surgical and medical settings [2–4]. A vast number of randomized clinical trials over the past 30 years provide undeniable evidence that primary thromboprophylaxis reduces deep vein thrombosis (DVT), pulmonary embolism (PE), and fatal PE. However, patients from psychiatric units have been always excluded from these previous studies, and data regarding the incidence of VTE in psychiatric units are lacking. Hospitalized psychiatric patients are nevertheless often exposed to factors known as predisposing factors of VTE such as immobilization, obesity, or increasing age. Psychiatric disorders themselves and treatment with antipsychotic medications have been associated with an increased risk of VTE in several observational studies using different methodologies [5–9]. Furthermore, historical literature suggests a relatively high prevalence of VTE in psychiatric patients. In 1966, Lal et al reported on consecutive autopsies of 357 patients diagnosed mainly with schizophrenia and chronic brain syndrome over the period 1961-1964 [10]. The prevalence of PE was 10 %, which was similar to the rate of PE found in all autopsies in the general hospital population. In a similar study of 343 autopsies in psychiatric patients, Kendel and Fodor found 98 (29%) cases of PE [11]. Therefore the incidence of VTE in psychiatric units is thought to be relatively high, but data are missing.

We report herein the results of a prospective cohort study designed to estimate the incidence of VTE in hospitalized psychiatric patients, and to assess the risk factors for VTE in this specific population.

Abbreviations: VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; CI, confidence interval; ICD, International Classification of mental and behavioral Disorders; CUS, compression ultrasonography.

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Methods

Study population

All consecutive patients, 18 years and older, admitted for a psychiatric disorder in psychiatric units of Brest University Hospital between March 2006 and March 2010, and in one psychiatric unit of Sainte-Anne Hospital in Paris between January 2008 and February 2009 were considered for inclusion in the study. To be eligible, patients had to plan to stay in hospital for at least seven days. Patients with symptomatic VTE at admission, or receiving long term anticoagulant treatment at therapeutic dose were excluded. Other exclusion criteria were patients placed into care involuntary and patient refusal.

Study design

At the time of admission, all eligible patients were asked to participate in the study. Absence of clinical signs and symptoms of VTE was verified. At Day 10, all participants were interviewed by a research nurse using a standardized questionnaire, and charts and medical records were reviewed extensively. Demographic data, general characteristics and conventional risk factors for VTE at admission were collected. All drugs taken at the time of admission were recorded as well as the given medications at Day 10. Mobility during hospitalization was assessed by estimation of the mean time of bed or chair rest per day including sleeping time.

The psychiatric diagnosis that led to hospitalization was recorded in the database using the International Classification of mental and behavioral Disorders (ICD.10 classification). Patients were evaluated for signs and symptoms of VTE during hospitalization and at Day 10. Any clinical suspicion of DVT or PE led to the relevant diagnostic procedure. A systematic compression ultrasonography (CUS) of the lower limbs was performed at Day 10 by a trained physician to detect asymptomatic DVT. All superficial and deep veins of the lower limbs were examined longitudinally and transversally, from the calf to the inferior vena cava, using duplex modality. The test was considered as positive in the absence of complete venous compressibility and the absence of blood flow. For patients who signed the specific consent, a blood sample was taken at Day 10. Factor V G1691A gene's mutation (Factor V Leiden), and the prothrombin G20210A gene variation, the most common inherited risk factors for VTE, were determined.

A phone follow-up was performed for all participants at Day 90. Patients or their relatives or their general practitioner were asked for symptomatic VTE events, hospitalization, use of anticoagulation and death since Day 10.

Objectives

The primary objective was the incidence of VTE by Day 10. VTE was defined as a composite of objectively confirmed symptomatic DVT (proximal or distal), fatal or symptomatic nonfatal PE, and asymptomatic DVT detected by systematic CUS at Day 10. In case of the presence of a venous thrombosis, the decision to treat the event with anticoagulant and the modality of the anticoagulant treatment were left at the discretion of the investigators.

Secondary objectives were the incidence of all VTE events at Day 90, and the assessment of clinical and biological risk factors of VTE in this specific population.

Symptomatic VTE required confirmation by objective imaging. All symptomatic VTE events between admission and Day 90 were centrally adjudicated by an independent adjudication Committee. Furthermore, the Committee reviewed all deaths between admission and Day 90 to determine if fatal PE could be the cause of death.

All predefined ultrasonographic images performed during the systematic CUS of the lower limbs at Day 10 were stored on videotapes and read by another skilled ultrasonographist. Inter-reader consensus was reached for any discrepant individual reading.

Statistics

Initial characteristics were described by median and range for quantitative variables, and by numbers and percentage for qualitative variables. Four classes of age and two of body mass index were *a priori* defined and used for description and univariate analysis.

Conventional risk factors for VTE were defined as the presence of surgery, or plaster cast, in the past three months, or active cancer, or hospitalization in medical unit in the past three months, or pregnancy and post-partum, or hormone replacement therapy, or contraception. Bed rest was defined as the mean time spent in bed or in chair per day, and then dichotomized in two classes according to the median.

Incidence, defined as the frequency of venous thromboembolic events among evaluable patients, was calculated at Day 10 and Day 90 with 95% confidence interval (CI).

Univariate analysis was performed to identify risk factors of VTE at Day 10 and Day 90. Fisher test was used to compare percentages. P value <0.05 was considered as significant.

We chose to perform subgroup analyses by age rather than multivariate analysis because of the well-established impact of age on VTE occurrence and the strong association of other variables with age. Only variables associated with VTE at Day 10 and Day 90 with p value ≤ 0.05 in univariate analysis were used for subgroup analyses. Age and psychiatric diagnoses were dichotomized according to univariate analysis results.

All statistical analyses were carried out using SAS Version 9.1.

Approvals

The protocol was approved by the independent ethics committee of our University Hospital and written informed consent was obtained from all patients, or their relatives or their guardian before inclusion. A specific consent was obtained to perform the blood sample including DNA-analysis.

Results

Patient Characteristics

During the study period, 397 patients from Brest University Hospital and 74 from Sainte-Anne Hospital were enrolled. Among the 471 included patients, 449 were evaluable for the primary outcome at Day 10, and 458 were followed-up until Day 90 (Fig. 1).

Table 1 described the initial characteristics of patients. The median age of the population was 60 years. Ninety patients presented dementia (ICD-10 codes F00 to F09), 114 patients presented schizophrenia, schizotypal and delusional disorders (ICD-10 codes F20 to F29), 148 patients presented mood disorder (ICD-10 codes F30 to F39), and 119 another psychiatric disorder. Only 11.1% of patients received no psychiatric drug at admission in psychiatric unit. Four patients (0.8%) received a prophylactic anticoagulant treatment at admission in psychiatric unit. Thromboprophylaxis was maintained at Day10 for only one of these four patients. For one patient, anticoagulant treatement at prophylactic dose started two days after admission in psychiatry.

Incidence of venous thromboembolism at Day 10

Four hundred forty eight patients had a systematic CUS of the lower limbs at Day 10 (median 10.0 days, interquartile range 8.0 to 11.0). No death occurred between admission and Day 10. One patient presented a symptomatic distal DVT confirmed by CUS before Day 10 and received anticoagulant for six weeks. The systematic CUS detected six distal DVT and three proximal DVT (Table 2). Overall, ten events occurred

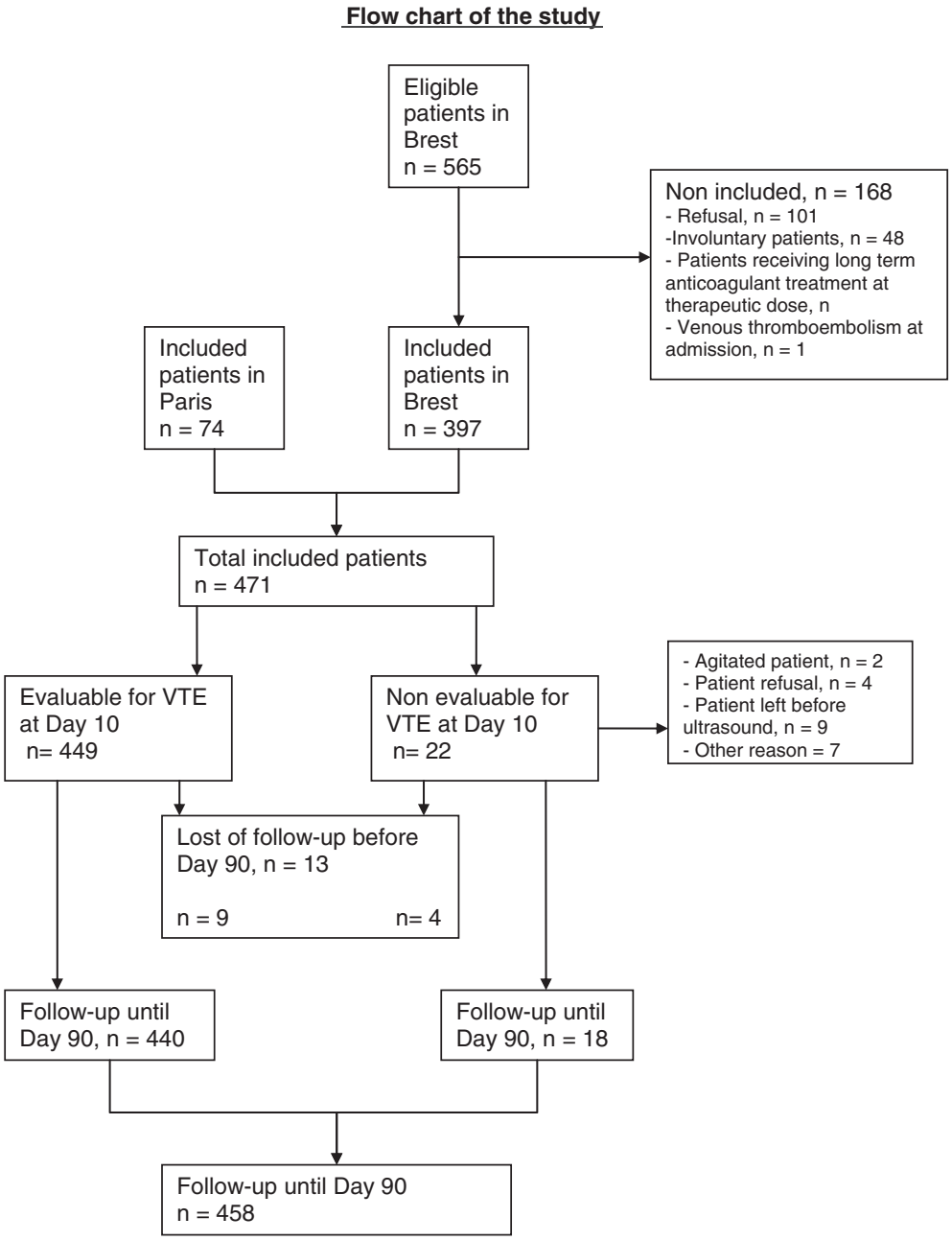

Fig. 1. Flow chart of the study.

leading to 2.2% incidence of VTE (95% CI, 1.1%–4.1%) at Day 10. Additionally, systematic CUS detected four isolated superficial vein thromboses and six isolated muscular thromboses. One of the patients with a muscular thrombosis detected on Day 10 and treated only with elastic stockings developed a PE between Day 10 and Day 90. All other patients for whom a thrombosis was detected on Day 10 did not present a new thrombotic event between Day 10 and Day 90 regardless of the use or not of an anticoagulant treatment.

Incidence of venous thromboembolism at Day 90

During the follow-up, 11 patients died. Among them, one patient had a symptomatic distal DVT two days before death, but fatal PE was not adjudicated to be the cause of death by the adjudication Committee. For the ten other patients, no autopsy was performed. The diagnosis of fatal PE was ruled out for four patients but could not be excluded for six patients by the adjudication Committee. Between Day 10 and Day 90, 11 patients received a prophylactic anticoagulant treatment for a few days, and two received an anticoagulant treatment at curative dose for another reason than VTE. Two patients had a symptomatic distal DVT, one had a proximal DVT, two had an isolated PE, and one had a proximal DVT associated with PE (Table 2). For four of these six patients, the venous thromboembolic event occurred during the initial stay in psychiatric unit (at Day 11, Day 16, Day 21 and Day 45). Then, six additional confirmed venous thromboembolic events occurred between Day 10 and Day 90. Therefore, the overall incidence of VTE at Day 90 was 3.5% (95% CI, 2.0% - 5.6%).

Risk factors for venous thromboembolism

Table 3 displays the frequency of venous thromboembolic events at Day 10 and Day 90 according to various clinical and biological factors, and Table 4 the frequency of venous thromboembolic events

Table 1
Clinical characteristics of the 471 included patients at admission.

Clinical characteristics of patients at admission	Median (Range) or n (%)
Age, years	60 (44–75)
Women	254 (53.9%)
Men	217 (46.1%)
Body mass index, kg/m^2	24.1 (21.6–27.4)
<25	265 (58.4%)
≥25	189 (41.6%)
Current smoking	165 (35.2%)
Alcoholism (current)	152 (32.3%)
Admitted from	
Home	386 (82.3%)
Institution	54 (11.5%)
Rehabilitation	5 (1.1%)
Psychiatric unit	2 (0.4%)
Hospital	22 (4.7%)
Psychiatric diagnosis retained for the current hospitalisation	
F0 (Organic, including symptomatic, mental disorders) or Dementia	90 (19.1%)
F1 (Mental and behavioural disorders due to psychoactive substance use)	75 (15.9%)
F2 (Schizophrenia, schizotypal and delusional disorders)	114 (24.2%)
F3 (Mood [affective] disorders)	148 (31.4%)
F4 (Neurotic, stress-related and somatoform disorders)	30 (6.4%)
F5 (Behavioural syndromes associated with physiological disturbances and physical factors)	2 (0.4%)
F6 (Disorders of adult personality and behaviour)	10 (2.1%)
F7 (Mental retardation)	1 (0.2%)
F8 (Disorders of psychological development)	1 (0.2%)
Current treatment at admission	
No psychiatric drug	52 (11.1%)
Antipsychotic drugs	211 (45.1%)
Antidepressant drugs	260 (55.3%)
Drugs for dementia	57 (12.1%)
Thymoregulators	59 (12.6%)
Anxiolytic drugs	288 (61.3%)
Sedatives or hypnotics	211 (44.9%)
Risk factors for venous thromboembolism present at admission	
Previous venous thromboembolism	28 (6.0%)
Surgical procedure in the previous three months	4 (0.9%)
Plaster cast immobilization of the lower limb in the previous three months	9 (1.9%)
Active cancer	9 (1.9%)
Pregnancy or post-partum	0 (0%)
Hospitalization in medical or surgical unit in the previous three months	45 (9.6%)
Hospitalization in psychiatric unit in the previous three months	89 (19.0%)
Cardiac insufficiency	9 (1.9%)
Respiratory insufficiency	3 (0.6%)
Oral contraception or hormone replacement therapy	13 (2.9%)
Factor V Leiden	19 (4.4%)
Mutation of prothrombin gene	15 (3.5%)

Table 2
Incidence of venous thromboembolic events.

Thromboembolic events at day 10	Evaluated patients at Day 10 n = 449
Venous thromboembolic events included in the primary outcome	10 / 449 (2.2%)
Symptomatic proximal DVT	0
Symptomatic distal DVT	1
Symptomatic PE	0
Fatal PE	0
Death	0
Asymptomatic DVT detected by ultrasonography	9 (6 Distal DVT and 3 Proximal DVT)
Other thrombotic events (not included in the primary outcome)	10 (4 isolated superficial vein thrombosis and 6 isolated muscular vein thrombosis)
Additional events between Day10 and Day90	**Evaluated patients at Day 90 n = 458**
Venous thromboembolic events	
Symptomatic proximal DVT	1
Symptomatic distal DVT	2
Symptomatic PE (± DVT)	3 (2 PE, 1 PE + Proximal DVT)
Fatal PE	0
Death	11
Total venous thromboembolic events at Day 90	16 / 458 (3.5%)
Symptomatic events at Day 90	7 / 458 (1.5%)
Asymptomatic proximal DVT and symptomatic events at Day 90	10 / 458 (2.2%)

DVT: deep vein thrombosis; PE: pulmonary embolism.

at Day 10 and Day 90 according to current psychiatric treatments at Day 10. Among all identified factors, age, bed rest, and diagnosis of dementia were associated with an increased risk of VTE at Day 10 and Day 90 in univariate analysis. Among psychiatric treatments, only drugs for dementia were significantly associated with VTE at Day 90.

Subgroup analyses (Table 5) showed that bed rest of 14 hours or more was a risk factor for VTE in patients under 75 years but not in patients 75 years and older. In contrast, diagnosis of dementia (F0 ICD-10 codes) was not associated with VTE in patients under 75 years but was reported to be an additional risk factor for VTE in patients 75 years and older, even if the association was not statistically significant.

Discussion

In the present study, the incidence of VTE (symptomatic VTE and asymptomatic DVT detected by systematic CUS) by Day 10 in hospitalized psychiatric patients was 2.2% (95% CI, 1.1%–4.1%). At Day 90, the incidence of VTE was increased to 3.5% (95% CI, 2.0%–5.6%). These results did not take into account the superficial and muscular vein thromboses or the potential fatal PE. The main factors associated with an increased risk of VTE at Day 10 and Day 90 were age, bed rest, and diagnosis of dementia. No association was found between antipsychotic drugs and VTE.

The rationale for use of thromboprophylaxis in medical and surgical units is based on solid principles and scientific evidence [1]. However, no relevant evidence has been reported for such utilization in psychiatric units. As a result, in such settings, thromboprophylaxis is used only on the basis of expert opinion or case reports and often extrapolated from medical settings [12–14]. Specific data on VTE incidence and risk factors are lacking in psychiatric units. We conducted this prospective study to help answering two main questions: Is there a rationale for use of systematic thromboprophylaxis in psychiatric units? Who are the patients at higher risk for VTE?

In our study, the global incidence of VTE at Day 10 in psychiatric units appeared low, ranging from 1.1% to 4.1%. In fact, without thromboprophylaxis, the incidence of objectively confirmed, hospital-acquired DVT is approximately 10 to 40% among medical or general surgical patients and 40 to 60% following major orthopaedic surgery [1]. The various study designs and methodologies could explain in part such difference: a systematic evaluation of VTE at Day 10 vs Day 15 or later, and the use of CUS vs phlebography or fibrinogen uptake test. However, when we consider the incidence of symptomatic VTE at Day 90, our results were close to those of the medical settings: 1.5 % in our study vs.1.3 % in the placebo group of the PREVENT study [15]. Furthermore, consistent with previous findings in medical settings [16,17], the incidence of VTE in psychiatric units was heterogeneous among subgroups. It was less than 2% in patients under 75 years, but was increased to 8.2 % (12.5% at Day 90) in older patients (≥75 years) with a diagnosis of dementia. In patients younger than 75 years, the risk for VTE appeared only in patients with reduced mobility defined in our study as a daily bed rest of 14 hours or longer. Our results from subgroup analyses suggest the need for further evaluation of thomboprophylaxis through randomized clinical trials in patients admitted in psychiatric units 75 years or older, and in those with important reduced mobility.

Table 3
Associations between clinical and biological factors and venous thromboembolic events at Day10 and Day 90.

Variables	VTE at Day 10 n = 449	p	VTE at Day 90 n = 458	p
Age, years				
<45	0 / 113 (0%)	0.05*	0 / 115 (0%)	0.002*
≥45<60	2 /102 (2.0%)		2 /100 (2.0%)	
≥60–<75	2 / 122 (1.6%)		4 / 127 (3.2%)	
≥75	6 / 112 (5.4%)		10/ 116 (8.6%)	
Sex				
Male	4 / 206 (1.9%)	0.76	5 / 207 (2.4%)	0.31
Female	6 / 243 (2.5%)		11 / 251 (4.4%)	
Psychiatric diagnosis				
F0 (Organic mental disorders)	5 / 86 (5.8%)	0.04*	8 / 90 (8.9%)	0.02*
F2 + F8 (Schizophrenia)	0 / 112 (0%)		1 / 108 (0.9%)	
F3 (Mood affective disorders)	3 / 141 (2.1%)		5 / 145 (3.4%)	
F1 + F4 + F5 + F6 + F7 (Others)	2 / 110 (1.8%)		2 / 115 (1.7%)	
Body Mass Index, kg/m^2				
<25	8 / 258 (3.1%)	0.21	10 / 264 (3.8%)	1
≥25	2 / 181 (1.1%)		6 / 181 (3.3%)	
Personal history of VTE				
Yes	0 / 28 (0%)	1	2 / 28 (7.1%)	0.26
No	10 / 421 (2.38%)		14 / 430 (3.3%)	
Classical risk factors for VTE				
Present	0 / 66 (0%)	0.37	1 / 69 (1.5%)	0.49
Absent	10 / 382 (2.5%)		15 / 388 (3.9%)	
Hospitalization in psychiatric unit in the previous 3 months				
Yes	2 / 85 (2.4%)	1	2 / 87 (2.3%)	0.75
No	8 / 363 (2.2%)		14 / 370 (3.8%)	
Current smoking				
Yes	1 / 162 (0.6%)	0.10	1 / 160 (0.6%)	0.01
No	9 / 286 (3.2%)		15 / 297 (5.1%)	
Bed rest				
≥14 hours per day	9 / 251 (3.6%)	0.05	14 / 257 (5.5%)	0.01
<14 hours per day	1 / 196 (0.5%)		2 / 199 (1.0%)	
Factor V Leiden				
Present	0 / 19 (0%)	1	1 / 19 (5.3%)	0.50
Absent	10 / 406 (2.5%)		14 / 406 (3.5%)	
Mutation of prothrombin gene				
Present	0 / 15 (0%)	1	0 / 15 (0%)	1
Absent	10 / 410 (2.4%)		15 / 410 (3.7%)	

* The p-value stands for the global comparison between the four groups.

Table 4
Associations between current psychiatric treatments at Day10 and venous thromboembolic events at Day10 and Day 90.

Current treatments at Day 10	VTE at Day 10 n = 449	p	VTE at Day 90 n = 458	p
Antipsychotic drugs				
Yes	5 / 264 (1.9%)	0.75	10 / 267 (3.8%)	0.80
No	5 / 184 (2.7%)		6 / 191 (3.1%)	
Antidepressant drugs				
Yes	5 / 307 (1.6%)	0.30	11 / 317 (3.5%)	1
No	5 / 141 (3.6%)		5 / 141 (3.6%)	
Drugs for dementia				
Yes	4 / 72 (5.6%)	0.06	7 / 74 (9.5%)	0.007
No	6 /376 (1.6%)		9 / 384 (2.3%)	
Anxiolytic drugs				
Yes	8 / 331 (2.4%)	1	12 / 340 (3.5%)	1
No	2 / 117 (1.7%)		4 / 118 (3.4%)	
Thymoregulator drugs				
Yes	3 / 88 (3.4%)	0.42	5 /92 (5.4%)	0.34
No	7 / 360 (1.9%)		11 / 366 (3.0%)	
Hypnotic or sedative drugs				
Yes	7 / 279 (2.5%)	0.75	11 / 285 (3.9%)	0.80
No	3 / 169 (1.8%)		5 / 173 (2.9%)	

Age and reduced mobility are well known risk factors for VTE, regardless of the underlying disease. Hence, it is not surprising to find these factors associated with VTE in patients hospitalized in psychiatric units. Diagnosis of dementia was also associated with a higher risk for VTE in our study. Nevertheless, the association was less apparent and seemed strongly linked to age. On the contrary, although previous studies suggested a possible link between schizophrenia and VTE [5], we did not find such association in our study. Finally, we did not find any association between antipsychotic drugs and VTE in contrast with abundant literature on the topic [5–9].

The strength of our study is that to our knowledge, this is the first prospective study specifically designed to evaluate the incidence of VTE in patients hospitalized in psychiatric units. The systematic evaluation at Day 10 by ultrasonography was possible for 95.3% of included patients, and follow-up was completed at Day 90 for 97.2%. There are a few limitations of the present study that need to be noted. Our study included a relatively large sample of psychiatric inpatients. However, the size of the sample and the number of VTE were not sufficient to assess conventional risk factors for VTE such as previous VTE or prothrombotic gene mutations. In regard to the drug exposure, our questionnaire was probably too restricted, recording only the type of drug at admission in psychiatry and at day 10. Drug dose and exposure duration were not recorded. We evaluated the mobility using the mean time of bed or chair rest per day during hospitalization. However, this measure did not distinguish between the bed rest and the physical restraint which is often needed for some patients in psychiatry. Our selection criteria were limited but led to a population not representative of the general population of psychiatric inpatients, especially in respect to the median age, relatively high in our study. Taking into account the strong impact of age observed in our study, we can not exclude an over-estimation of VTE incidence in psychiatric units at Day 10. Furthermore, because some variables were linked to age (e.g. diagnosis of dementia and current smoking), it was difficult to analyze them independently. On the contrary, since the adjudication Committee could not exclude fatal PE as the cause of death for six patients, the incidence of VTE observed at Day 90 might have been under-estimated.

The incidence of VTE at Day 10 in psychiatric units seemed to be lower than in medical or surgical units. However, the incidence of symptomatic VTE at Day 90 was consistent with the incidence of VTE observed in medical units. Patients at higher risk for VTE when hospitalized in psychiatric units were older, especially those with dementia, and those with prolonged bed rest. For these patients, we believe that a thorough risk-benefit assessment of thromboprophylaxis use should be considered through randomized clinical trials.

Conflict of interest statement

No competing financial interests to disclose.

Table 5
Results from stratified analyses according to age (<75 years or ≥75 years).

Variables	VTE at Day 10	p	VTE at Day 90	p
Age≥75 years				
Bed rest				
≥14 hours per day	5 / 88 (5.7%)	1	8 / 92 (8.7%)	1
<14 hours per day	1 / 23 (4.3%)		2 / 23 (8.7%)	
Dementia				
Yes	5 / 61 (8.2%)	0.22	8 / 64 (12.5%)	0.18
No	1 / 51 (2.0%)		2 / 52 (3.8%)	
Age<75 years				
Bed rest				
≥14 hours per day	4 / 163 (2.5%)	0.05	6 / 165 (3.6%)	0.01
<14 hours per day	0 / 173 (0%)		0 / 176 (0%)	
Dementia				
Yes	0 /25 (0%)	1	0 /26 (0%)	1
No	4 / 312 (1.3%)		6 / 316 (1.9%)	

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