

Risk and prophylaxis of venous thromboembolism in hospitalized psychiatric patients. A review

Anna Wilkowska¹, Hanna Kujawska-Danecka², Adam Hajduk²

¹Department of Adult Psychiatry, Medical University of Gdansk

²Department of Internal Diseases, Connective Tissue Diseases and Geriatrics,
Medical University of Gdansk

Summary

Venous thromboembolism (VTE) is a frequent dangerous complication occurring during hospital treatment with total annual incidence of 70–200 per 100,000 citizens. Venous thromboembolism includes deep vein thrombosis (DVT) and pulmonary embolism (PE). Pulmonary embolism is responsible for about 10% of hospitalization-related deaths and is the most common avoidable reason for deaths in hospitals.

Psychiatric inpatients are particularly vulnerable to an increased risk of VTE due to their limited mobility, the use of restraints, catatonia, communication difficulties, and the use of antipsychotics. Patients with chronic psychiatric conditions like schizophrenia and recurrent affective disorders have significantly higher somatic comorbidity. This population of patients requires specific approach to VTE prophylaxis during hospitalization.

This article offers an insight into issues related to thromboembolism, and presents validated diagnostic tools and VTE prophylaxis strategies. The paper includes the review of available research on VTE in patients hospitalized for psychiatric reasons. Considering the scarcity of specific studies in this population we highlight the necessity to follow the available general medical guidelines for psychiatric inpatients.

Key words: venous thromboembolism, deep vein thrombosis, pulmonary embolism, psychiatric hospitalization

Introduction

Venous thromboembolism (VTE) is a serious problem in hospitalized patients and it is related to increased mortality and prevalence. Psychiatric inpatients are a special group. They are exposed to such risk factors as limited mobility [1], the use of antipsychotics [2, 3], restraints [4], and catatonia [5]. Elderly patients are a special risk group, since they often suffer from comorbidities, dehydration, and cancer. The diagnosis of

VTE in psychiatric patients can be delayed due to communication-related difficulties [6] or the attribution of symptoms to non-somatic causes [7].

The available guidelines concerning prophylaxis fail to take into account hospitalized psychiatric patients and no Polish prophylaxis standards have been developed for this group of patients so far. Since the average length of stay of psychiatric patients in hospitals is longer in Poland than in the majority of other EU countries, the problem of VTE seems to be particularly important [8].

This paper aims at offering an insight into the issues related to venous thromboembolism in the area of its diagnosis and the possible prophylaxis strategies, as well as at reviewing the available research carried out on the population including psychiatric patients.

Definition

VTE is a condition in which a thrombus forms in a vein. It most often forms in deep veins of the lower extremities, causing deep vein thrombosis (DVT). A thrombus may travel from its original site, moving with the blood, which is referred to as an embolism. Venous thrombosis often gives no symptoms, rarely causing pain or leg swelling. Fragments of the thrombus may travel with the stream of blood, reaching the lungs and causing a pulmonary embolism (PE) [1].

Diagnosis

Deep vein thrombosis should be suspected in any patient suffering from an unexplained swelling of either extremity accompanied by pain, increased warmth, and reddening. Pain related to DVT often has the form of a painful cramp of the calf or thigh.

Pulmonary embolism frequently starts with dyspnea and pleuritic pain in the chest or back. It may cause increasing fatigue, exertional dyspnea, faintness, or sudden death. As such symptoms may occur in many diseases, therefore the thrombosis risk factors should be assessed for a given patient [9].

Epidemiology

The incidence of VTE significantly increases along with age, with the condition affecting more often younger women than men (< 45 years of age), and the reversing trend in elderly population [10]. With the total annual incidence of 70–200 per 100,000 citizens, VTE is the third most frequently occurring cardiovascular disease [11–14]. It is estimated that the annual DVT and PE incidence for Poland is, respectively, about 57,000 and 36,000 cases [15]. About 50% of cases of symptomatic DVT involve asymptomatic pulmonary embolism, and up to 70% of symptomatic pulmonary embolism cases involve asymptomatic DVT [12]. PE is responsible for about 10% of hospitalization-related deaths and is the most common avoidable reason for deaths

in hospitals [16–18]. More than 50% of patients hospitalized for a variety of reasons are exposed to an increased risk of deep vein thrombosis and/or pulmonary embolism [19]. The correct VTE prophylaxis is considered to be the most important intervention increasing the patients' safety [20].

Risk factors

Among the numerous VTE risk factors there are genetic and acquired factors, including environmental ones (Table 1) [9, 15]. The risk factors can also be divided according to the degree of the risk of VTE occurrence. VTE low risk factors (odds ratio OR < 2) include hospitalization of the mobile patient, immobilization in bed for > 3 days, obesity, and advanced age. Medium-risk factors (OR 2–9) include hospitalization of the non-ambulatory patient, a catheter placed into a large vein, cancer, in particular during chemotherapy, heart failure, or respiratory failure. The hospitalization of a patient requiring intensive medical care always involves a high risk of VTE (OR > 10) [15, 20, 21]. It is believed that VTE is a consequence of an interaction between patient-related factors (which are normally permanent) and factors to do with a variety of circumstances (which are normally temporary) [20]. However, in 25–40% of patients, VTE may occur without any known risk factors [10, 11].

Table 1. Selected VTE factors [8, 9, 20]

Selected VTE factors	
Genetic factors	Antithrombin deficiency, protein C deficiency, protein S deficiency, factor V Leiden, prothrombin gene mutations, hyperhomocysteinemia
Acquired factors	Age > 40 years, antiphospholipid syndrome, nephrotic syndrome, tobacco smoking, obesity (BMI > 30 kg/m ²), heart failure (NYHA III, IV), respiratory failure, sepsis, inflammatory bowel diseases, cancers, myeloproliferative syndrome, autoimmune diseases (connective tissue diseases, vasculitides), infections, non-surgically treated severe adult diseases (e.g., serious pneumonia)
Environmental factors	Major surgeries (particularly within the pelvis, abdominal cavity or lower extremities), trauma, long-term immobilization (travelling, limb paresis), pregnancy, hormonal therapy (e.g., taking oral contraceptives), a catheter placed into a large vein, chemotherapy

Assessment of VTE risk

The level of the risk of VTE depends on many factors, including the patient's individual characteristics and his/her current condition, comorbidities, and the pharmacological treatment administered at a given time. According to the Polish guidelines for the prophylaxis and treatment of VTE, the VTE risk should be assessed during every hospitalization [15]. It is recommended that the assessment be performed with the help of the appropriately prepared, validated scales evaluating the most important risk factors

[9]. Tools for the assessment of the risk of VTE in hospitalized patients include the Padua prediction score [22]. This score uses 11 predisposing factors, which may score from 1 to 3 points (Table 2). A total score of 4 or more points is tantamount to a high risk of VTE and indicates the necessity to implement thromboprophylaxis [22, 23].

Table 2. Padua score – assessment of the risk of VTE in hospitalized patients [8, 22]

Characteristics	Points
Active cancer (patients with metastases to regional lymph nodes or with distant metastases, who were treated with chemotherapy or radiotherapy during the last 6 months)	3
History of VTE (apart from superficial thrombophlebitis)	3
Immobilization (expected necessity to stay in bed – with the ability to use the bathroom/toilet – due to the patient's disability or following doctor's instructions for ≥ 3 days)	3
Diagnosed thrombophilic condition (deficiency of antithrombin, protein C or S, factor V Leiden, G20210A prothrombin gene mutation, or antiphospholipid syndrome)	3
Recent (≤ 1 month) trauma or surgery	2
Age ≥ 70 years	1
Heart failure or respiratory failure	1
Recent myocardial infarction or ischemic stroke	1
Acute infection or rheumatologic disorder	1
Obesity (BMI ≥ 30 kg/m ²)	1
Hormonal treatment	1
Interpretation ≥ 4 points – high risk of VTE	

Diagnostic strategies for VTE

DVT should be suspected in any patient displaying an unexplained edema, pain, reddening, or increased warmth of a limb. However, it should be stressed that clinical symptoms are highly varied and are marked by low sensitivity and specificity, especially when assessed separately [9, 24]. For this reason, validated tools such as the Wells' score, taking into account clinical symptoms and selected predisposing factors, are used for the assessment of the clinical probability of DVT [25, 26]. D-dimer is assessed additionally, but it should be noted that this particular test is marked by a high sensitivity and low specificity [27]. In the case of a suspected VTE, the specificity of the D-dimer systematically decreases along with age to almost $< 10\%$ in patients > 80 years [28]. An increase in the specificity in those persons who are elderly can be achieved by adjusting the cut-off point to age (age $\times 10$ ug/l above 50 years) [29, 30]. In patients with a low probability of DVT (on the basis of the Well's score), the correct D-dimer test result makes it possible to exclude DVT [31, 32], while in patients with a probable DVT (based on the Wells' score), ultrasound of the veins of the legs should be performed to exclude or confirm DVT. The result of the D-dimer test in

such patients, however, is not conclusive. In this case, thromboprophylaxis should be administered until the imaging test is performed [10, 31].

Table 3. Wells' score – assessment of the clinical probability of DVT [31]

Characteristics	Number of points
Cancer (treated or diagnosed during the last 6 months)	1
Paralysis, paresis, or recent immobilization of the lower extremity in plaster	1
Recently bedridden for >3 days or a major surgery during the last 4 weeks	1
Local pain along the deep venous system of the lower extremity	1
Edema of the entire lower extremity	1
Shin diameter > 3 cm in comparison to the leg displaying no symptoms (measured 10 cm below tibial tuberosity)	1
Pitting edema (more extensive on the symptomatic extremity)	1
Documented history of DVT	1
Collateral (non-varicose) superficial veins present	1
Another diagnosis equally or more probable than DVT	-2
Interpretation: clinical probability	Total
Low probability	≤ 1
Probability	≥ 2

A pulmonary embolism should be suspected in patients displaying sudden dyspnea, chest pain (often pleural pain), faintness or hemoptysis, especially in patients with symptoms of DVT [20]. Although hypotonia and shock are rare, they are related to the markedly decreased hemodynamic reserve and indicate a high (> 15%) risk of an early death [33]. In view of the low specificity of signs and symptoms, a pulmonary embolism may remain non-diagnosed, be entirely asymptomatic, or be diagnosed accidentally during diagnostic examinations related to another disease or during autopsy [10, 34].

The clinical probability of a pulmonary embolism is assessed for example on the basis of the Wells' score, which is based on 7 easy-to-obtain information items, such as data from the interview and clinical symptoms. On the basis of the total number of points scored, the clinical probability for PE is assessed as low, medium, or high [35]. The share of patients in which a confirmed PE can be expected amounts to about 10%, 30% and 65% respectively for the low, medium and high probability [36].

Table 4. Wells' score – assessment of the clinical probability of PE [35, 37]

Characteristics	Rule for scoring on the basis of clinical decision	
	Original version Wells [35]	Simplified version Gibson [37]
History of PE or DVT	1.5	1
Heart rate ≥ 100 bpm	1.5	1

table continued on the next page

Surgery or immobilization in the last 4 weeks	1.5	1
Hemoptysis	1	1
Active cancer	1	1
Clinical symptoms of DVT	3	1
Alternative diagnosis less likely than PE	3	1
Interpretation: Clinical probability		
Three-tier model		
Low	0–1	No data
Medium	2–6	No data
High	≥ 7	No data
Two-tier system		
PE unlikely	0–4	0–1
PE likely	≥ 5	≥ 2

Source: ESC guidelines concerning the diagnosis and management of acute pulmonary embolism in 2014. *Kardiologia Polska* 2014; 72, 11: 997–1053.

Prophylaxis

Under the Polish guidelines of 2012, internal strategies for the assessment of the risk and prophylaxis of VTE should be developed and implemented in every hospital, while guidelines in an electronic or paper form should be in force in the entire hospital. Research results show that the primary prophylaxis in the form of the administration of heparin or mechanical methods is effective and more economical than the treatment of complications [38]. Apart from the early mobilization, there are two main methods of thrombosis prophylaxis: pharmacology and mechanical methods.

Mechanical methods

The mechanical methods include graduated compression stockings (or the use of an appropriately applied short stretch compression bandage) and sequential compression devices (SCD), comprising a sleeve put on the limb and an electric pneumatic pump, which sequentially fills the sleeve segments with air [39]. The effectiveness of the mechanical methods depends on their appropriate application. What is stressed in particular is that the size of the stockings and sleeve for SCD should be appropriately selected and that they should be used for most of the day. Stockings should be taken off only briefly, when necessary (e.g., for a bath), while the SCD sleeve – when the patient walks [40]. Before recommending the use of compression stockings, contraindications should be considered, including peripheral artery disease, status post peripheral artery bypass graft surgery, peripheral neuropathy, circulatory failure, limb edema or pulmo-

nary edema resulting from circulatory failure, skin lesions, non-typical limb size or the limb shape preventing appropriate stocking adjustment [1].

Pharmacology

Recommendations for the pharmacological practice related to VTE include the use of one of anticoagulants, such as unfractionated heparin (UFH), low-molecular-weight heparins (LMWH, including dalteparin, enoxaparin, nadroparin), selective inhibitors of factor Xa (fondaparinux, rivaroxaban, apixaban), or vitamin K antagonists (acenocoumarol, warfarin), and a direct oral thrombin inhibitor (dabigatran) [39]. Medicines most frequently mentioned in the recommendations in the context of the treatment of patients in nonsurgical departments include heparins and fondaparinux [15, 23].

The selection of the particular anticoagulant should be based on a number of factors (patient's preferences and the possibility to cooperate with that patient, the route and frequency of administration, and treatment cost). In Poland, the most frequent daily clinical practice involves the use of low-molecular-weight heparins administered in the doses recommended by the manufacturer. The group of patients requiring a particular caution in the use of heparins is that of patients suffering from chronic kidney disease, especially the elderly ones, with diabetes and a high-risk of bleeding. Since medicines from the heparin group are eliminated through the kidneys, it is necessary to reduce the dose in the case of significantly impaired function; with the GFR below 30 ml/min/1.73 m², a 50% dose reduction is recommended [40]. It is worth adding that the advantages of the use of a prophylactic dose of anticoagulants clearly outweigh the risk of clinically significant hemorrhagic complications [39].

Authors point out that the selection of the method of thromboprophylaxis should be based on the risk of hemorrhagic complications. In the case of patients with a high risk of bleeding, it is recommended that mechanical methods are used – at least initially, until the risk of bleeding is decreased. In the case of patients in whom the risk of bleeding is not high, both methods – the pharmacological and the mechanical one – should be used [15].

There are no detailed Polish recommendations applying to hospitalized psychiatric patients. The Polish recommendations of 2012 described a category of patients admitted to hospital due to an acute, non-surgically-treated disease. Admission to a psychiatric unit is not usually caused by an acute somatic disease. However, in the course of hospitalization, many patients, especially elderly ones or ones with a history of somatic diseases, may experience an acute condition (such as infection), which, in particular when combined with immobilization and the existing VTE risk factors, may increase the risk of thromboembolic complications.

The use of force is a special clinical situation, especially in the context of patients of over 65 years of age. It is worth remembering that the restraint of an elderly patient increases the risk of thromboembolic complications – not only directly, but also

through an increased risk of an acute condition, including an infection, in particular a respiratory one [41].

On the basis of the recommendations of the Polish working group, it is recommended that for a non-surgically-treated hospitalized patient a prophylactic dose of LMWH, a small dose of unfractionated heparin, or fondaparinux (for patients with an increased risk of venous thromboembolism) be used. If the risk is low (as assessed on the basis of the Padua Prediction Score), such a practice is not recommended. The Polish guidelines also do not recommend the use of thromboprophylaxis in patients experiencing bleeding or belonging to the high-risk group for bleeding. Therefore, the assessment of the risk of bleeding seems to be as important as the assessment of factors increasing the risk of thromboembolic complications. The authors of the Polish guidelines underline that, although subjective and difficult, it is indispensable for the safety of thromboprophylaxis in the daily medical practice – also in psychiatric units [15].

According to the guidelines of the American College of Chest Physicians, the risk of bleeding is the highest in the case of active stomach or duodenal ulcers, serious bleeding in the course of the last 3 months, thrombocytopenia with the level of platelets below $50 \times 10^9/l$, or a liver insufficiency of $INR > 1.5$. Other factors increasing the risk of bleeding include: age ≥ 85 years, severe renal failure ($GFR < 30 \text{ ml/min/1.73m}^2$), chronic inflammatory joint disease, active cancer, and male gender. It is worth stressing that most of these factors are simultaneously risk factors for VTE [23]. Meta-analysis by Streiff and Lau [42] also mentions the age of 40–80 years and moderate renal impairment of $GFR 30\text{--}59 \text{ ml/min/1.73m}^2$. The NICE guidelines also take into account active bleeding, lumbar puncture during 4 hours before or 12 hours after examination, uncontrolled hypertension of $> 230/120 \text{ mmHg}$ and congenital coagulation disorders [1].

Psychiatric patients – research review

There are fewer data concerning the prevalence and the course of VTE in hospitalized psychiatric patients. The available publications focus on the risk factors specific for this group, the relationship between VTE and the type of mental disorder, as well as the use of psychotropic medications.

One of the prospective studies has found that the prevalence of thrombosis is particularly high (about 10%) for hospitalized patients aged over 75 years suffering from dementia. The increased risk of VTE in younger patients only applied to those whose mobility was limited ($\geq 14 \text{ h}$ in bed). The authors indicate age and limited mobility as the two most significant risk factors in this group of patients and stress the need for randomized trials to determine the risk and the advantages of using the prophylaxis in this group [43].

The use of restraints is a potential factor increasing the risk of thrombosis in hospitalized psychiatric patients. The authors of a Japanese study found that despite the use of routine prophylaxis, DVT was discovered in 11.6% of patients to whom

a restraint was applied. In all the cases, the course of thrombosis was symptomless. Risk factors included sedation, a longer restraint, a lower dosage of antipsychotic medications, and hospitalization due to comorbidities during 90 days prior to the inclusion in the study [44].

Neuroleptic malignant syndrome is an acute condition, which possibly increases the risk of thrombosis [45]. However, apart from casuistic works, there have been no reports in this area. Catatonia is yet another special clinical condition increasing the risk of VTE in the form of a fatal pulmonary embolism. An analysis of literature showed 20 cases of PE confirmed during an autopsy of patients with diagnosed catatonia. Pulmonary embolism occurred after 2 weeks of persistent symptoms of catatonia – suddenly, without preliminary symptoms [5]. The authors also presented two new cases of a sudden death of patients with diagnosed catatonia. According to the Japanese researchers, the prevalence of DVT in patients with catatonia reaches as much as 25% [46].

As it is commonly known, psychological stress causes an increase in blood coagulation by activating the adrenergic system [47]. Taking into account that the element of stress is present in every acute psychiatric condition, increased coagulation should be expected in patients with various diagnoses. In one of the studies, the measurement of markers of thrombogenesis demonstrated that patients with schizophrenia experiencing psychotic symptoms display increased indicators of thrombogenesis even prior to the introduction of their treatment with antipsychotic medications [48].

Studies carried out on members of the Taiwanese population showed that patients with diagnosed schizophrenia suffer from deep vein thrombosis and pulmonary embolism about twice as often as others [49]. It has also been demonstrated that schizophrenic patients chronically treated with antipsychotics suffer from global hypercoagulability, which may be related to an increased risk of VTE [50].

The authors of a retrospective study carried out on a Canadian population of mothers with diagnosed schizophrenia discovered an increased risk of various complications, including VTE, during pregnancy (aOR 1.72 95% CI 1.04–2.85) [51].

VTE is diagnosed 1.3 times more often in patients with depression [52]. There is also data indicating the importance of symptoms of depression in an increased risk of recurrent thrombosis, regardless of other prognostic factors. The risk may be increased even in the case of only slightly exacerbated symptoms of depression. A 3 point increase in the total HADS score was related to a 44% higher risk of recurrent VTE (OR 1.44 95% CI 1.02–2.06) [53].

An increased risk of pulmonary embolism was also discovered in bipolar disorder (incidence rate ratio IRR) 1.61; 95% CI (1.38, 1.88) [54]. An increased coagulation (increased level of vWF antigen and the activity of factor VIII) was also described in serious chronic post-traumatic stress disorder [55].

The use of antipsychotics, especially clozapine and weak first-generation antipsychotics, increases the risk of thrombosis from 2 to 10 times, depending on the type of the used medicine [56, 57]. An Austrian program of monitoring of serious adverse

drug reactions in hospitalized psychiatric patients taking antipsychotics discovered an incidence of VTE corresponding to 34 cases per 100,000 admissions, with the VTE most often diagnosed in persons aged over 65 years diagnosed with mood disorders. The highest risk was related to butyrophenones and atypical antipsychotics [58]. A study carried out on a large population of patients treated on an outpatient basis demonstrated that the risk of VTE was 32% higher in persons to whom antipsychotics were recommended during the last 24 months than in the control group. The effect persisted despite taking into account some other risk factors (OR 1.32, 95% CI 1.23 to 1.42). The estimated increase in the incidence of VTE per 10,000 patients treated over 1 year was 4 (3–5) in all age groups, and 10 (7–13) in patients older than 65 years [59].

The mechanism of increase of the risk of thrombosis by first-generation antipsychotics is possibly based on an enhanced platelet aggregation. The second probable mechanism is related to the presence of anticardiolipin antibodies [60, 61].

There is an increasing amount of evidence concerning such increased risk also in the case of the use of second-generation antipsychotics such as olanzapine or risperidone [62, 63]. In one of the already quoted works, it was demonstrated that the risk of VTE was greater in the case of second-generation antipsychotics (aOR 1.73 for atypical antipsychotics, and 1.28 for first-generation antipsychotics) [59]. Other studies indicate a 2–2.7 times higher incidence of VTE in patients taking atypical antipsychotics [2, 64]. However, it is difficult to clearly determine whether the relationship between taking antipsychotics and the increased risk of VTE results directly from the effects of such medicines or indirectly, from some other risk factors such as obesity or a low physical activity [65].

An increased risk of VTE was also discovered in patients taking antidepressants (aOR 1.59; 95% CI 1.27–2.00). The increased risk was in particular applicable to tricyclic antidepressants, 5HT_{2A} inhibitors, and serotonergic antidepressants [66]. Taking into account the serious risks to do with VTE, patients taking psychiatric medications should be informed of this possible complication and the symptoms they should be particularly sensitive to [56].

Despite the clearly higher risk of VTE in the population of psychiatric patients, preventive actions are undertaken rarely. One of NICE's (National Institute for Health and Care Excellence) audits demonstrated that the risk of VTE was not assessed in 63–83% of patients [67]. On the basis of the guidelines concerning other groups of patients, taking into account risk factors specific for psychiatric patients, Malý et al. [68] developed a scoring system aimed at the prevention of VTE in the Czech Republic. In Poland, such a protocol has not yet been developed.

There is little data concerning the effectiveness of the prevention of VTE in hospitalized psychiatric patients. De Hert et al. [69] confirmed the effectiveness of anticoagulants in the prophylaxis of DVT in schizophrenic patients. In a large German hospital, 40 mg of enoxaparin sodium per 24 hours is administered as a standard to patients immobilized for longer than 24 hours. Hilger et al. [70], who examined more than 1,000 cases of the restraint of patients in this hospital in 2012

and 2013, have not discovered a single case of VTE, confirming the effectiveness of such a procedure.

Despite the scarcity of data concerning the prophylaxis of VTE in hospitalized psychiatric patients in everyday medical practice, general medical guidelines should be followed. Venous thromboembolism is a serious, often non-diagnosed, while simultaneously easy-to-avoid complication affecting the treatment and prognosis of patients with mental disorders.

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Address: Alina Wilkowska
Department of Adult Psychiatry
Medical University of Gdansk
80-211 Gdańsk, Dębinki Street 7
e-mail: ali.wilkowska@gmail.com