

The risk of venous thromboembolism in patients with heart failure

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Aim. To quantify the risk of venous thromboembolism (VTE) in hospitalized patients, depending on the severity of heart failure (HF).

Material and methods. Current cross-sectional study included 132 patients hospitalized in the cardiology department in 2019. All participants were divided into 2 groups: group 1 (n=48) — patients with class I-II HF; group 2 (n=84) — patients with class III-IV HF. A total quantitative assessment of the VTE risk was carried out according to the Caprini risk scoring method.

Results. All patients hospitalized in the cardiology department, regardless of HF class, had a higher and highest risk of VTE and required prophylactic anticoagulation. Highest VTE risk had 85% of patients with class I-II HF; 97,6% — patients with a class III-IV HF. Mean score of ≥ 10 was observed in every fifth patient. Atrial fibrillation requiring long-term anticoagulant therapy was observed in 51,5% of patients. There were no absolute contraindications for parenteral prophylactic anticoagulation at the time of hospitalization in the study population.

Conclusion. All patients admitted to the cardiology department had a higher and highest risk according to the Caprini

risk score, regardless of HF class. More than half of the patients had indications for long-term anticoagulant therapy. The remaining patients required the parenteral prophylactic anticoagulation.

Key words: heart failure, venous thromboembolism, prevention.

Relationships and Activities: not.

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Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, according to epidemiological studies, annually cause about 10 million deaths worldwide and take third place after myocardial infarction and stroke [1]. Heart failure (HF) is one of the most common risk factors for VTE, especially in hospitalized patients [2]. Meta-analysis by Tang L, et al., which included 46 studies, showed that the overall incidence of VTE in this population was 2,48% (95% confidence interval (CI) 0,84-5,61); without thromboprophylaxis — 3,73% (95% CI 1,05-7,31) and with thromboprophylaxis — 1,47% (95% CI 0,64-3,54). In general, the relative risk of VTE for hospitalized patients with HF was 1,51 (95% CI 1,36-1,68) [3]. An assessment of VTE risk in all hospitalized patients older than 40 years in Russia is recommended to be carried out in accordance with the Russian clinical guidelines for the diagnosis, treatment and prevention of venous thromboembolism (2015) [4]. This document includes the Caprini risk score (2005) for the most important VTE risk factors [5]. The individual score allows assigning patient to a certain category: low risk (0-1 points), moderate risk (2 points), higher (3-4 points) and highest risk (≥ 5 points). With higher and highest VTE risk and without high bleeding risk, the patient should receive prophylaxis with unfractionated heparin, low-molecular-weight heparins or fondaparinux sodium, if the patient does not receive long-term anticoagulation therapy for other indications. At moderate risk, non-pharmacological interventions are recommended. According to this score, congestive HF for at least 1 month is estimated at 1 point. However, the combination of HF and other independent characteristics (age ≥ 60 years, body mass index $> 25 \text{ kg/m}^2$, limited excursion, varicose veins and others) resulting in categorizing a patient with class I-II HF as the higher and highest risk of VTE.

On the other hand, factors such as concomitant liver and kidney failure, single and dual antiplatelet therapy use, and gastrointestinal pathology increase the risk of bleeding in this population. In this regard, the adequate determination of indications for primary prevention remains relevant issue.

The aim of the study was to quantify the VTE risk in hospitalized patients, depending on the severity of HF.

Material and methods

Type: cross-sectional study with an assessment of VTE risk at the time of hospital admission. Study population was patients hospitalized in the cardiology department of Chelyabinsk City Clinical Hospital № 1 from September 1 to November 1, 2019. Inclusion criteria were HF and presence of echocar-

diography data records for the last year. Exclusion criteria were acute coronary syndrome, active bleeding, as well as cancer, including its history in the last 5 years. We used continuous sampling method involving 132 patients. In addition to the factors related to Caprini risk score, the following were taken into account: nosological structure and characteristics of HF (stage, class) according to Russian clinical guidelines (2018) [6]; indications for the long-term anticoagulation therapy (atrial fibrillation, thrombosis history), comorbidity, stage of chronic kidney disease, and current therapy, including antiplatelet agent use.

This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The medical ethics committee of South Ural State Medical University (Russia) approved this study (protocol № 12, 29.08.2019). All participants gave written informed consent.

Statistical processing was carried out using MedCalc statistical software (version 19.1.3, Belgium). Quantitative parameters data are presented as a median and an interquartile range (Me; Q25-Q75). To assess the differences of quantitative parameters between two groups, Mann-Whitney U-test was used. Qualitative parameters are described by absolute and relative frequencies with assessment of intergroup differences using the Pearson's chi-squared test, and at expected frequencies < 5 — using two-tailed exact Fisher's test. Differences were considered significant at $p < 0,05$.

Results

The study included 132 patients, which were divided into 2 groups: group 1 ($n=48$) — patients with class I-II HF; group 2 ($n=84$) — patients with class III-IV HF. Group 1 was dominated by patients with preserved and mid-range ejection fraction (85,4% vs 48,8%, $p_{1-2} < 0,001$). At the same time, every second patient in group 2 had HF with reduced ($< 40\%$) ejection fraction (51,2% vs 14,6%, $p_{1-2} < 0,001$). The distribution depending on HF stages was as follows: group 1 — 3 patients with stage I ($p_{1-2} = 0,046$), 45 patients with stage IIa ($p_{1-2} < 0,001$); group 2 — 36 patients with stage IIa, 45 patients with stage IIb ($p_{1-2} < 0,001$), 3 patients with stage III ($p_{1-2} > 0,05$).

Clinical characteristics of patients are presented in Table 1.

Indications for hospitalization in both groups were hypertensive crisis, atrial fibrillation and other cardiac rhythm disturbances. The mean age of patients in both groups was > 70 years, which already made it possible to assess the VTE risk at 2 points. Patients in group 2 had higher mean age, smoking prevalence, as well as significantly higher incidence

Table 1

Clinical characteristics of patients with class I-II and III-IV HF

Parameter	Group 1 (n=48)	Group 2 (n=84)	P
Age, years (Me; Q25-Q75)	70,5 (56,5-80,5)	74,5 (64,0-82,5)	<0,001
Gender, men, n (%)	13 (27)	32 (38)	0,20
Smoking, n (%)	9 (18,8)	29 (34,5)	0,055
Body mass index >25 kg/m ²	41 (85,4%)	79 (94%)	0,098
Hypertension, n (%)	46 (95,8)	72 (85,7)	0,07
Coronary artery disease. Angina pectoris, n (%)	17 (35,4)	75 (89,3)	<0,001
History of myocardial infarction, n (%)	13 (27,1)	48 (57,1)	<0,001
Heart defects, n (%)	10 (20,8)	33 (39,3)	0,03
Atrial fibrillation, n (%)	20 (41,7)	48 (57,1)	0,088
Diabetes, n (%)	10 (20,8)	22 (26,2)	0,491
Chronic obstructive pulmonary disease, n (%)	3 (6,3)	4 (4,8)	0,715
Chronic kidney disease with glomerular filtration rate <60 ml/min/m ² , n (%)	5 (10,4)	13 (15,5)	0,599
Anemia, n (%)	18 (37,5)	65 (77,4)	<0,001
Ischemic stroke (up to 1 month old)	1 (2,1%)	2 (2,4%)	0,612
Varicose veins	30 (62,5%)	69 (82,1%)	0,098
Bed rest	4 (8,3%)	39 (46,4%)	<0,001

of coronary artery disease, acquired heart diseases, and limited excursion ≥ 3 days. In total, 68 people (51,5%) had atrial fibrillation without statistical differences between the groups. Chronic venous disorders $\geq C2$ (CEAP classification) were observed in 62% of patients in group 1 and 82% in group 2, which made it difficult to diagnose HF-related congestion. Anemia, mainly mild hypochromic, was 2 times more common in group 2. No differences were found in the incidence of inflammatory respiratory and gastrointestinal diseases.

The total quantitative risk assessment of VTE by Caprini score is presented in Table 2.

All patients hospitalized in the cardiology department, regardless of HF, belonged to the higher and highest risk categories of VTE and required prophylactic anticoagulation. In the group of patients with class III-IV HF, more than 97% of patients were at high risk; every fifth patient had an average score of ≥ 10 . However, only 1 patient had a history of VTE (deep vein thrombosis) in group 2 and none in group 1. A total of 51,5% of patients had atrial fibrillation and the average CHA₂DS₂-VASc score was 4,5; all these patients had indications for long-term anticoagulant therapy. In group 1 of the remaining 28 patients with sinus rhythm, 12 people had indications for antiplatelet therapy due to coronary artery disease; in group 2, of 36 people with a sinus rhythm, 30 patients had indications for single antiplatelet therapy and 3 people — for dual antiplatelet therapy due to a history of percutaneous coronary intervention. It

Table 2

Caprini risk score categories in hospitalized patients with HF

Parameter	Group 1 (n=48)	Group 2 (n=84)	P
Low, n (%)	0	0	>0,05
Moderate, n (%)	0	0	>0,05
Higher, n (%)	7 (14,6)	2 (2,4)	0,077
Higher, n (%)	41 (85,4)	82 (97,6)	0,077
Mean score ≥ 10	4 (8,3)	22 (26,2)	0,013

should be noted that there are currently no evidence-based studies on the adequacy of antiplatelet therapy for the VTE prevention in hospitalized patients, including those with HF. There were no any absolute contraindications for the administration of prophylactic anticoagulation at the time of hospitalization in both groups.

Discussion

Epidemiological studies in various populations showed a high variability in the prevalence of VTE in HF patients, which is often due to asymptomatic cases of thrombosis, difficulties in timely diagnosis, and the similarity of symptoms of VTE and HF [3, 7]. The contribution of VTE to the all-cause mortality in HF patients is also not fully determined. In a pro-

spective study by Bounameaux H, et al. it was shown that pulmonary embolism may be a primary cause of death in 3-10% of HF patients [8]. When analyzing the national database in the USA for the 2000-2013, the authors noted an increase of VTE prevalence from 0,76% in 2000 to 1,46% in 2013 and decrease in VTE mortality during hospitalizations with HF from 10,8% in 2000 to 7,2% in 2013 [9]. The main pathogenetic mechanisms for increasing the VTE risk in hospitalized cardiovascular patients can be endothelial injury and endothelial dysfunction, dysfunction of anticoagulant protein C system with increased plasma concentrations of pro-inflammatory cytokines (interleukin-6, tumor necrosis factor, etc.), PAR activation, blood stasis with reduced cardiac output, tissue injury with expression of tissue factor activating coagulation cascade, fibrinolysis slowing [10]. Additional risk factors for VTE in HF patients can be: old age, immobilization, infections, frequent central venous catheter use, implantation of pacemakers and defibrillators, which increase the risk of infectious complications and, in general, hypercoagulability. It should be noted that identification of some factors by Caprini score (for example, thrombophilia) is difficult and inappropriate in the general population, and was not performed in our study. However, it must be remembered that underestimation of genetic factors in some cases can lead to an undercount of VTE risk.

The results obtained in our study in patients with class III-IV congestive HF is confirmed in several other studies. So, in the MEDENOX study (Prophylaxis in Medical Patients with Enoxaparin), an almost 2-fold increase in the VTE incidence in patients with class IV compared with class III HF was detected (21,7% vs 12,3%) [11]. This was one of the first evidence-based studies on the efficacy and safety of low-molecular-weight heparins (enoxaparin at a dose of 40 mg) in the primary prevention of VTE. Direct oral anticoagulants (DOACs) for the primary prevention of VTE in hospitalized non-surgical patients were studied in randomized, double-blind, placebo-controlled studies: ADOPT (Apixaban Dosing to Optimize Protection From Thrombosis) — apixaban at a dose of 2,5 mg twice daily up to 30 days [12]; MAGELLAN (Multicenter, Randomized, Parallel Group Efficacy and Safety Study for the Prevention of Venous Thromboembolism in Hospitalized Acutely Ill Medical Patients Comparing Rivaroxaban with Enoxaparin) - rivaroxaban at a dose of 10 mg for 35±4 days [13] and APEX (Acute Medically Ill VTE) Prevention With Extended Duration Betrixaban Study) — betrixaban at a loading dose of 160 mg and then 80 mg for 35-42 days [14]. All drugs were compared with enoxaparin at a dose of 40 mg for 6-14

days. Longer-term use of DOACs was due to high incidence of VTE in the first month after hospital discharge. The proportion of HF patients in this study was 38-44%. Analysis of these three studies by Yami M, et al. demonstrated greater efficacy of longer-term use of DOACs compared with the standard course of enoxaparin for symptomatic VTE (relative risk — RR 0,63; 95% CI 0,46-0,88) and all VTEs in general (RR 0,78; 95% CI 0,68-0,90), but without significant differences in asymptomatic VTE (RR 0,84, 95% CI 0,70-1,01) and VTE-related mortality (RR 0,70, 95% CI 0,45-1,08). However, the use of DOACs was accompanied by a higher bleeding risk. So, the RR of major bleeding for the three drugs was 1,99 (95% CI 1,08-3,65); RR of clinically relevant non-major bleeding — 1,86 (95% CI 1,16-2,97) [15]. Betrixaban had the highest safety. In the Russian Federation, an indication for the DOACs use for the primary VTE prevention in hospitalized non-orthopedic patients has not been recorded.

We have not revealed absolute contraindications for the prophylactic anticoagulation at the time of hospital admission. At the same time, it is necessary to take into account the high incidence of anemia in the studied population, which required a further differential diagnosis between anemia of chronic disease and iron deficiency anemia and finding the source of bleeding.

Study limitations. The limitations of our study may be due to with a small sample size that does not allow us to estimate the absolute and relative risks of VTE in patients with HF. Cross-sectional study design does not allow dynamically monitoring and evaluating various interventions for the VTE in HF patients. Another limitation may be the features of diagnostics in all patients with HF, which did not allow assessing high-risk thrombophilia, as well as the inability to perform venous ultrasound, which could help identify patients with asymptomatic lower extremity venous thrombosis.

Conclusion

Thus, all patients hospitalized in the cardiology department had a higher and highest risk of VTE by Caprini score. In the group of patients with class I-II HF, 85% of patients had a highest risk, and with class III-IV HF — 97,6% of patients; mean score of ≥ 10 was observed in every fifth patient. Indications for long-term anticoagulant therapy, mainly for atrial fibrillation, were in 51,5% of patients. The remaining patients, with the exclusion of a high bleeding risk, required parenteral prophylactic anticoagulation.

Relationships and Activities: not.

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