THE ROLE OF STATINS IN DEEP VEIN THROMBOSIS

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THE ROLE OF STATINS IN DEEP VEIN THROMBOSIS (Abstract): Deep vein thrombosis (DVT) represents the formation of a blood clot in one of the deep veins of our body, predominantly occurring in the legs. According to international guidelines, the goal of the treatment in deep vein thrombosis is to prevent the progression and the recurrences of thrombotic process. The aim of this article is to explain the pathogenetic mechanism of deep vein thrombosis and the benefits of statins in such a disease. The vasoprotective effects of statins are related to their anti-thrombotic and anti-inflammatory properties. The administration of statins is associated with a lower incidence of venous thromboembolism (VTE) in the general population. It also helps in reducing the frequency of recurrences, being prescribed after an optimal 6 to 12 month anticoagulation. The study of these properties creates new opportunities for the use of statins in the prevention of post-thrombotic syndrome and recurrent venous thromboembolism (VTE).

Key words: STATINS, VENOUS THROMBOSIS, THROMBOEMBOLISM.

About 1 in a 1000 adults develops annually a Deep Vein Thrombosis (DVT). The incidence increases from 0.01% in young adults to 1% in people over 60. More than half of these events involve deep vein thrombosis in the inferior vena cava basin. In 25% of untreated cases, the thrombi extend towards proximal veins. Consequently, in the case of proximal DVT the risk of asymptomatic or symptomatic pulmonary thrombo-embolism increases to 5% and that is more likely to occur if the emboli are caused by proximal thrombi. In order to decrease the risk of fatal pulmonary emboli, the early diagnosis and prompt treatment of DVT are essential.

DVT pathogenesis mentions three broad categories of factors also known as Virchow’s triad: endothelial injury, venous stasis and hypercoagulability. The vessel wall injury interferes with the coagulation inhibition function and prevents the local fibrinolytic process of the endothelium. Venous stasis, caused by patient immobilization or vein obstruction blocks the clearance and dilution of activated coagulation factors and finally the congenital or acquired thrombophilia, leading to hypercoagulation.

The venous thromboembolism pathogenesis is multifactorial, often resulting from a combination of several risk factors. The most common risk factors for secondary venous thrombosis include cancer,
surgery, immobilization for long periods of time, fractures, paralysis, pregnancy, birth and use of estrogens or of selective estrogen receptor modulators. Still, for approximately 30% of the patients the cause of DVT occurrence remain inexplicable, the same as in the case of spontaneous or idiopathic thrombosis.

THE CORRELATION BETWEEN DEEP VEIN THROMBOSIS AND ATHEROSCLEROSIS PROCESS

The existence of an association between atherosclerosis and idiopathic venous thrombosis was demonstrated for the first time in 2003 by Professor Prandoni and his research group. In a clinical case-control study about half of the patients diagnosed with idiopathic acute venous thrombosis developed signs of asymptomatic atherosclerosis (at least one carotid atherosclerotic plaque, estimated by scanning the carotid arteries) (1). The essence of this association is still unknown: could venous thrombosis be induced by atherosclerosis or do the two conditions have a parallel development, in the presence of common risk factors? Certain factors correlated to the development of both pathologies have been identified: old age, obesity, diabetes mellitus, the metabolic syndrome (2). On the one hand the prothrombotic state in atherosclerosis can favor venous thrombotic events. In the case of atherosclerosis (ASVD) the evaluated elements are: the plaque aggregation activation, the blood coagulation activation and the increase of fibrogenesis. All these elements can lead to thrombotic complications both at the arterial level and in the venous system. On the other hand, both clinical conditions can be simultaneously triggered by certain biological stimuli, responsible for the activation of coagulation and swelling in the vascular system. Thus, the excess of fibrinogen, von Willebrand factor antigen, plasminogen tissue activator, D-dimers, coagulation factor VII, C-reactive protein (CRP), tumor necrosis factor-α (TNF-α) and interleukin, that circulate in the blood, cause a pro-coagulant and pro-inflammatory state both in the venous and the arterial system (3). We cannot exclude the probability that both hypotheses are true, representing thus two pathophysiologic scenarios for the development of venous thrombosis. These hypotheses are confirmed by vast authentic evidence, resulted from important clinical studies. The Cardiovascular Health Study (2009) proved that asymptomatic atherosclerosis represents a risk factor for VTE (venous thromboembolism) (4), while Atherosclerosis Risk in Communities Study (ARIC) showed that that the anti-plaque treatment and/or other antithrombotic treatments plays an important role in the prevention of venous thromboembolism dysfunctions in patients with clinically manifest atherosclerosis (5). Another study assessed the relapse rates for DVT, postthrombotic damage severity and mortality 10 years after the first VTE episode, in patients previously included in the Duration of Anticoagulation (DURAC) study. After ten years the mortality rate due to acute myocardial infarction (AMI) or fatal ictus cerebri was significantly higher (approximately 28%) in patients with spontaneous VTE, if compared with patients with secondary VTE and with the general population (6). Other randomized control trials (P. Becattini; P. Prandoni; N. Bova) demonstrate a higher incidence of symptomatic atherosclerosis (ischemic cardiomyopathy, acute myocardial infarction, cerebral vascular accident, atherosclerosis of the peripheral arteries, ischemic cardiac failure, sudden death) in patients with idio-
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pathic venous thrombosis if compared with patients with secondary VTE and with the general population.

THE ROLE OF STATINS IN PRIMARY AND SECONDARY PREVENTION OF VTE (VENOUS THROMBOEMBOLISM)

The objectives of DVT treatment, according to international guidelines, consist in the prevention of the thrombotic process progression as well as the prevention of relapses. Treatment is initiated with unfractionated heparin or low molecular weight heparin, followed by an indirect anticoagulant. The administration of direct anticoagulants will be ceased within 7-10 days while indirect anticoagulants will be administered for at least another six month, if there are no contraindications. The risk of hemorrhage occurrence represents the main criteria in the limitation of oral anticoagulant treatment duration. In most patients, the benefits of long-term prophylactic treatment of recurrent VTE can be compromised by an increased risk of bleeding, especially after 12 months of continuous administration. This fact has consequently demanded the research of alternative strategies for the secondary prevention of VTE, which have recently led to discussions about HMG-CoA reductase inhibitors (7). HMG-CoA reductase inhibitors represent one of the most commonly used groups of drugs. The special attention they are granted is justified not only by their high efficiency as hypolipidemic agents. Numerous experimental in vitro, in vivo and clinical studies have confirmed in the past years several beneficial effects resulted through mechanisms that have no connection with the changes in lipid metabolism and are commonly named pleiotropic effects. The vasoprotective effect of statins is ensured by these properties, the anti-thrombotic and anti-inflammatory activity being the most important. These characteristics may lead to new perspectives regarding the post-thrombotic syndrome and VTE recurrences prevention.

The discovery of connections between atherosclerosis and venous thrombosis lead to the initiation of clinical and experimental studies meant to estimate the role of statins in diminishing the VTE risk. A randomized, placebo-controlled, multicenter trial, Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), included 17,800 practically healthy subjects that received 20 mg of rosuvastatinum or placebo, its main purpose being the study of statin efficiency in the decrease of major cardiovascular events rate. The assessment of pulmonary embolism or VTE primary episodes occurrence constituted one of the secondary purposes of the trial (8). After an average surveillance period of 1.9 years (up to a maximum of 5 years) it was concluded that rosuvastatinum administration reduces the symptomatic VTE risk with 43% for the practically healthy subjects participating in the study, when compared to the administration of placebo, no matter if the episode was idiopathic or was caused by a well-known factor.

Specialized literature (9) mentions a series of clinical trials that explore the alternative strategy hypothesis in the VTE prevention and provide scientific evidence of the influence of statins on VTE risk. The multicenter, observational, prospective randomized controlled clinical trial, Heart and Estrogen/Progestin Replacement Study, that included 2,763 female subjects provided data that proved a significant decrease of 50% of VTE risk in patients receiving statins. Statins determined a decrease of 22% of the relative risk of DVT.
occurrence in patients over 65, in an observational retrospective trial that included a total of 125,000 patients with no history of atherosclerosis, venous thrombosis or cancer (10). Certain authors of case-control clinical trials mention a venous thrombosis risk decrease with approximately 26%-58% following statins therapy (11). In the population-based case-control study (MEGA study) that assessed 10,500 subjects, including 4,500 patients with primary episode of venous thrombosis in the lower limbs or pulmonary embolism, the use of statins, regardless of the active substance or the duration of the treatment, was associated with a significant 55% decrease of primary and recurrent DVT, proving to have a better effect in combination with the main treatment (13). An estimation of the venous thrombotic risk (by means of vascular Doppler) in 2,427 post-menopausal female patients aged between 30 and 89, of which 465 had a first episode of venous thrombosis, showed a significantly lower risk for the subjects who received statins (12). It was at the same time noticed that the risk rate was influenced by simvastatin, regardless of the dose, but remained unchanged in the case of pravastatin administration, probably due to differences in action at the level of coagulation activation internal mechanisms, blocked by lipophilic simvastatin and uninfluenced by hydrophilic pravastatin (13). Another such study assessed 5,824 VTE patients and a control group consisting of 58,000 subjects without a history of venous thrombosis. The outcomes lead to two important conclusions: patients with a history of cardiovascular events are exposed to a certainly higher VTE risk, especially within the first 3 month following an acute myocardial infarction or stroke; constant administration of statins is associated with a lower relative risk of VTE (approximately 26%) (14). The outcomes of a retrospective study that assessed 593 patients with myocardial infarction or ischemic cerebrovascular accident (CVA) showed that statins can be efficient for VTE prevention in atherosclerosis patients, the DVT risk being three times higher in patients who do not receive statin therapy (15). The effect depends on the dosage, being more significant in case of high doses (50% lower risk if compared with the standard 20 mg statin doses).

The use of statins in the case of patients with solid tumors (colon, pancreas, breast, ovarian, renal and cerebral cancer) was associated with a relatively low probability of VTE occurrence (8% as opposed to 21% in the group without statins), including VTE and pulmonary embolism. Regression analysis provided an identical result, regardless of other factors involved, such as smoking habits, the presence of metastases, chemotherapy administration, immobilization, aspirin administration (16). In that particular context, there were some attempts to compare the effect of statins to the effect of fibrates, in a randomized control trial assessing 1,354 patients hospitalized for idiopathic venous thrombosis (17). The use of statins resulted in a significantly lower risk of recurrent VTE episodes, while fibrate administration was associated with a higher risk (0.53 vs. 1.88) (18). In another study – the MEGA study – other groups of hypolipemiant (non-statins) caused an increase of 22% in primary or recurrent venous thrombosis risk, compared to patients who did not received hypolipemiant drugs (19). In the above mentioned observational case-control study the female patients were administered statins, fibrates, bile acid sequestrants or niacin; a lower risk of venous thrombosis was signaled only in the group that received statins (20).
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The specialized literature does not produce any evidence regarding VTE aggravation or risk increase due to statins therapy. The beneficial action of HMG-CoA reductase inhibitors, in the venous thrombosis pathology, is ensured by the anti-plaquetary, anticoagulant, profibrinolytic, anti-inflammatory, anti-cytokinetic, anti-oxidant and hypolipemiant effects that ensure all of them, the proper functioning of the vascular endothelium and finally contribute to maintaining an optimal balance between pro-thrombotic and fibrinolytic mechanisms. Manifestations of anti-thrombotic effects of statins consist in the inhibition of plaquetary aggregation, a decrease in thrombin production, the blockage of pro-thrombin activation, of the factor V and factor XVIII, the inhibition of the tissue factor with an important part in the maintenance of extrinsic coagulation cascade, the decrease of D-dimers seric level (marker of the prothrombotic state and independent risk factor for VTE recurrences), the stimulation of fibrinolytic activity through the intensification of tissue plasminogen activator (tPA) and the diminishing of plasminogen activator inhibitor-1 (PAI-1) (21). Since inflammation is known to be one of the lesion mechanisms of the vascular wall and consequently an important factor in the destabilization of coagulation-fibrinolysis processes, we cannot neglect the role of the anti-inflammatory pleiotropic effect of statins in preventing recurrent primary venous thrombosis and the development of the post-thrombotic syndrome. Statins reduce the level of inflammation markers: C-reactive protein (in the CARE, PRINCE, AFCAPS/TexCAPS studies), tumoral necrosis factor-α, -1β and -2 interleukin, fibrinogen, CD40L ligand. There exists an association between the high risk of VTE, the increase of plasmatic values of triglycerides (over 1.05 mmol/l) and the decrease of HDL cholesterol (under 1.79 mmol/l) (22). In this context, statins are benefic due to their well-known effect on the serum lipid spectrum.

CONCLUSIONS

VTE is associated with high morbidity and mortality. The optimal remedy for the prevention and treatment of VTE should combine the advantages of efficiency, minimal bleeding risk and ease of administration. Statins seem to meet the last two criteria, yet their efficiency has not yet been fully demonstrated. They cannot be suggested as alternative anti-thrombotic remedies instead of oral anti-coagulants in the treatment of acute of sub-acute venous thrombosis. Yet, clinical studies demonstrate that the use of statins is rational as far as VTE prophylaxis is concerned, long-term secondary prophylaxis included. Statin therapy is associated with a decrease of VTE incidence in the general population as well as with a decrease of the incidence of recurrences, when administered after the recommended 6-12 month anticoagulant treatment. Still, more studies are needed in order to prove the efficiency of this drug for such a condition and create the opportunity to extend the indications for this group of drugs for certain population categories.

REFERENCES


