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CHARACTERISTICS OF THE STUDY GROUP AND DYNAMICS OF PATHOGENETIC MARKERS ON THE BACKGROUND OF DIFFERENT ANTI-COAGULATION MODES

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Abstract: Statins are a potential means of preventing venous thromboembolism (VTE), complementing traditional anticoagulants, without concomitant bleeding-related complications. The purpose of this study was to compare the prothrombotic activity of different classes of lipid-lowering drugs in an active comparative study and determine whether there is a link between the use of statins, fibrates/niacin and procoagulant factors.Currently, taking statins is associated with lower plasma FXA levels than taking fibrates/niacin. The effect on blood clotting factors may partly explain the benefits of statin therapy in the primary and secondary prevention of VTE.
Keywords: Study group characteristics, Pathogenetic markers, Anticoagulation therapy, Anticoagulation modes, Coagulation parameters, Hemostasis markers, Thrombotic risk.

Introduction. It is estimated that the incidence of venous thromboembolism (VTE) is 1-2 cases per 1000 person-years among people of European descent [1]. Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the so-called statins, are a class of lipid-lowering drugs that are widely used to prevent atherosclerosis [2]. There is increasing evidence that statins are a promising means of preventing VTE, complementing anticoagulants without concomitant bleeding-related complications [3,4,5,6,7,8,9]. In addition to lowering lipid levels, statins have anti-inflammatory and antioxidant properties [10, 11].

Moreover, mainly in the course of in vitro studies and observations, it was found that they can have a positive effect on the walls of blood vessels and have antithrombotic properties [12, 13]. These include decreased expression of tissue factor and thrombin production, impaired thrombin-catalyzed procoagulant reactions, including fibrinogen cleavage and activation of factors (F) V and FXIII, decreased activity of FVII and FVIII, increased expression of endothelial thrombomodulin and increased fibrinolytic activity, manifested in decreased expression of plasminogen activator inhibitor (PAI)-1 and increased expression of tissue plasminogen activator (tPA) [14, 15]. In addition, it is assumed that it has an antiplatelet effect, immediately and delayed inhibiting platelet activation, adhesion, and aggregation, although previous research could not confirm these results in vitro [15, 16].

A recent randomized trial showed that 1 month of treatment with rosuvastatin at a dosage of 20 mg/day leads to an improvement in coagulation parameters, primarily to a decrease in factor VIII levels, in patients with previous DVT compared with those who did not take statins [17]. Given that the effect of drugs is not necessarily common to all representatives of the class, the reduction of procoagulant factors under the influence of rosuvastatin may not apply to other statins currently on the market. It is known that different types of statins reduce the level of low-density lipoproteins in different ways, reduce the manifestations of atherosclerosis and inflammation. The lowest effect is observed in those

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taking pravastatin, followed by those taking simvastatin and atorvastatin, and the greatest in those taking rosuvastatin [16, 18, 19].

A meta-analysis of randomized clinical trials has shown that there is a dose-effect relationship in which rosuvastatin, which is most effective in stopping or slowing the development of atherosclerosis, dyslipidemia, and inflammation, also provides the most significant reduction in the risk of venous thrombosis [20]. We sought to find out whether there is a relationship between statin use and indicators of procoagulant factors in participants of the Dutch Obesity Epidemiology Study (NEO) [20].

Materials and methods. We conducted a cross-sectional analysis of the baseline indicators of the NEO study participants who took lipid-lowering drugs (statins or fibrates/niacin) and compared their prothrombotic activity in an active comparative study. The NEO study is a cohort study involving 6,671 people aged 45-65 years living in Leiden (in the west of the Netherlands). Most of the participants had a body mass index (BMI) of 27 kg/m2 or higher. During the initial examination after a night of fasting, blood samples were taken from participants in test tubes containing 0.106 M sodium citrate (Sarstedt, Numbrecht, Germany). Plasma was obtained by centrifugation at 2500 × g for 10 minutes at room temperature and stored in aliquots at -80 °C until analysis. Fibrinogen activity was measured using the Claus method. In addition, activity FVIII:C, FIX:C, FXI:C was measured by mechanical clot detection on an ACL TOP 700 analyzer (Werfen, Barcelona, Spain). All the analyses were performed by laboratory technicians who were unaware of the status of the samples.

Statistical analysis. The general characteristics of the participants were presented in the form of averages (± standard deviation) or figures (with percentages). Since niacin/fibrates do not have antithrombotic properties [23], participants taking drugs of this class were considered as a control group. The average values of blood clotting factors in participants taking any statins were compared with the control group using linear regression and presented as an average difference. The magnitude of the effect was shown with 95% confidence intervals (CI). One assumption is that there is no preference in prescribing a lipid-lowering drug to a particular patient and that clinical characteristics should be evenly distributed among participants. Considering that this assumption may be too bold, we included age, gender, smoking, BMI, hypertension, diabetes and common cardiovascular diseases (myocardial infarction, angina pectoris, congestive heart failure) as potential distorting factors in the regression analysis. All statistical analyses were performed in SPSS version 22.0.

Results. The general characteristics of the participants (n = 1043) who took drugs to reduce lipid levels at the initial stage are shown in Table 1. Most of them took five different classes of statins. A small subgroup (n = 22) took niacin/fibrates as drugs to reduce lipid levels. More than two thirds of the participants reported that they had smoked (in the past or currently), and almost half of them suffered from hypertension (systolic blood pressure (BP) ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg). Approximately one third of the patients suffered from diabetes (according to their own words, they had diabetes mellitus, which they treated, or fasting plasma glucose > 7 mmol/l) or impaired glucose tolerance (6.1–7 mmol/l).

The overall analysis showed that all blood clotting factors were lower in those taking statins than in those taking fibrates/niacin, with the exception of fibrinogen, which was higher in the groups taking statins (Table 2). The difference was most noticeable in FXI:C, which

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showed almost 17 IU/dl lower levels in patients taking statins than in patients taking fibrate/niacin (mean difference was 17.1 IU/dl, 95% CI -30.0 to -4.3). Adjusting for potential distorting factors did not change the results (the average difference was 18.3 IU/dl, 95% CI − 27.3--9.4). In addition, those who are currently taking statins have lower levels of FIX and FVIII (adjusted mean difference − 11.3 IU/dl, 95% CI − 23.2 to 0.4) and − 15.8 IU/dl, 95% CI − 31.6 to 0.003, respectively) with borderline statistical significance. Those taking rosuvastatin have lower levels of FVIII and FIX than those taking other types of statins, although these tests are hampered by a small number of participants.

Discussion. We found that those who are currently taking statins have a level of FXI:Plasma C is lower than that of those taking fibrates/niacin. The results of our study confirm the conclusions of the STAtins Reduce Thrombophilia (START) study, according to which a one-month course of treatment with rosuvastatin at a dose of 20 mg per day in patients with previous VTE reduced the level of coagulation factors VII:C, FVIII:C, FXI:C and the von Willebrand factor (vWF):Ag in plasma compared to those who did not take statins [17]. We also showed that those who are currently taking statins have an FXI level.:C is 18.3 IU/dl (from 9.4 to 27.3) lower, and the level of FVIII:C is 15.8 IU/dl (-0.003 to 31.6) lower than that of those taking fibrates/niacin as lipid lowering drugs. The observed difference appears to be more related to the use of rosuvastatin than other types of statins, as they consistently had lower levels of FVIII:C and FXI:C is almost 18 IU/dl and about 15 IU/dl lower than in those who did not take statins. The effect of statins on the level of blood clotting factors has previously been noted in various studies. In the Multi-Ethnic Study of Atherosclerosis (MESA) cohort, consisting of people who did not suffer from cardiovascular diseases or active cancer, those who took statins had lower levels of D-dimer and FVIII than those who did not take statins [14]. Simvastatin treatment of patients with impaired glucose tolerance and hypercholesterolemia decreased the levels of fibrinogen, FX:C, vWF:Ag, PAI-1 and FVII activity in plasma. This also led to an increase in prothrombin time and activated partial thromboplastin time. The simultaneous use of ezetimibe with simvastatin had a synergistic effect on blood clotting parameters. In addition, ezetimibe has been reported to enhance and stabilize the anticoagulant effect of warfarin, especially when combined with statins [26]. Similarly, rosuvastatin, but not pitavastatin, increased the international normalized value (INR) in healthy volunteers taking warfarin.

A Dutch study evaluating the short- and long-term effects of new statins on the dosage of vitamin K antagonists (AVCS) has shown that patients taking statins require lower doses of AVCS to achieve their INR target. The most significant effect was observed when taking simvastatin and rosuvastatin. It was also noted that pravastatin enhances the anticoagulant effect of dalteparin. On the other hand, the simultaneous use of rosuvastatin and warfarin in a small number of healthy people did not affect the pharmacodynamics of warfarin in a stable state. It has also been reported that rosuvastatin did not inhibit thromboxane-dependent platelet aggregation in patients with a history of VTE.

Moreover, a one-year course of treatment with atorvastatin or simvastatin in patients with coronary heart disease did not significantly affect the measured coagulation parameters, although the fibrinolytic profile improved in patients taking these drugs. There are also reports that statins do not affect the level or activity of FVII and FVIII. Although the differences in coagulation rates observed in our research group, in particular FVIII and FIX, between those who took statins and those who took fibrates/niacin, seemed to be more related to rosuvastatin, we were unable to identify differences between rosuvastatin and other types

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of statins, probably due to- due to the small number of participants. It is believed that the side effects of drugs are not necessarily common to all drugs, especially if the main mechanism of action of the drug and the mechanism of side effects differ.

Thus, there is reason to believe that the antithrombotic properties of statins may be inherent only to some of them. In most observational studies and randomized controlled trials, it was concluded that the use of rosuvastatin was associated with the most significant (almost 40%) reduction in the risk of VTE compared with those who did not take statins. Moreover, in the Dutch cohort of patients with a history of pulmonary embolism (PE), potent statins with a lipid-lowering effect (for example, rosuvastatin) had the most significant effect in preventing recurrence of PE (hazard ratio (HR) 0.29, 95% CI 0.07-1.16), followed by statins of moderate efficacy (e.g., atorvastatin; HR 0.44, 95% CI 0.3–0.65) and low efficacy (e.g., pravastatin; HR 0.88, 95% CI 0.5–1.54) [43]. Despite these results, several reports emphasize the lack of association between the type of statins and the risk of first or repeated VTE. Finally, we showed that, unlike other coagulation factors measured, fibrinogen levels in those who took statins were higher than those who took fibrates/niacin, although the difference was statistically insignificant. Since fibrinogen is associated with pro-inflammatory and procoagulant effects, statins could be expected to reduce fibrinogen levels. A previous study reported that fibrinogen levels decreased after 12 weeks of treatment with simvastatin at a dosage of 20 mg per day in patients with impaired fasting glucose levels and hypercholesterolemia.

Conclusion. Currently, taking statins is associated with lower levels of FXA in blood plasma. The type of statin taken may make a difference, although further randomized controlled trials with a much larger number of participants are needed.

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