Received: 22 March 2022 | Accepted: 29 March 2022

DOI: 10.1111/jth.15728

COMMENTARY

Commentary on "Elevated plasma levels of plasminogen activator inhibitor-1 are associated with risk of future incident venous thromboembolism": A new role for plasminogen activator inhibitor-1—An inhibitor of fibrinolysis predicts future venous thromboembolic events and links them to obesity

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Venous thromboembolism (VTE) is an overarching term for two thrombotic pathologies, namely deep vein thrombosis (DVT) and pulmonary embolism (PE). Behind coronary heart disease and stroke VTE is the third most common cause of cardiovascular morbidity worldwide.[1,2] The ISTH Steering Committee for World Thrombosis Day has identified VTE as a major global disease burden and as age is a major risk factor for VTE this burden will continue to grow in importance due to increasing life expectancy worldwide.[2] The incidence for VTE among Caucasians is between 104 and 183 per 100 000 person years, whereas these values for DVT and PE, respectively, are 45–117 and 29–78 per 100 000 person years.[3–6] Feeding data from six European countries Cohen and colleagues calculated the total number of symptomatic VTE events with 460 000 cases of DVT and 295 000 cases of PE per year, resulting in 370 000 deaths.[7] These data underline the urgent need to, on the one hand, identify reliable predictors for VTE to prevent such events by detecting persons at risk to suffer from future VTE and to, on the other hand, find and characterize possible therapeutic targets for prevention and treatment.

The fibrinolytic system is critically involved in a variety of pathophysiological processes such as, for example, tumor growth and metastasis, cell proliferation and migration, matrix remodeling and angiogenesis.[8] Its name, however, relates to its role in the dissolution of blood clots through the degradation of fibrin.[9] Thereby plasminogen activators (PAs) such as urokinase-type PA (u-PA) or tissue-type PA (t-PA) cleave the zymogen plasminogen into its active protease plasmin, which then in turn degrades fibrin. Plasminogen activator inhibitor-1 (PAI-1) is the major inhibitor of PAs and thus of fibrinolysis.[9] High plasma levels of PAI-1 have been identified as a risk factor for myocardial infarction (MI).[10,11] The possible association with VTE, however, remains blurred. Two large population-based studies produced opposite results. While the Longitudinal Investigation of Thromboembolism Etiology (LITE) study reported no link between future VTE and high PAI-1 plasma levels in 308 VTE patients, the authors of the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) study, performed with 770 VTE patients and 743 controls, found an association of high PAI-1 plasma levels and VTE.[12,13]

In this issue of JTH, Frischmuth and colleagues set out to shed more light on these controversial findings.[14] For their nested control study, the authors enrolled participants of the Tromsø Study as their source population. The Tromsø Study is a single center, population based cohort with repeated health checks of inhabitants of the Norwegian town of Tromsø.[15] Of the 27 158 individuals participating

Manuscript handled by: Sabine Eichinger

Final decision: Sabine Eichinger, 29 March 2022

in the fourth survey of the Tromsø Study between 1994 and 1995, the authors identified 462 VTE cases of which 383 cases were finally analyzed and compared to 782 age- and sex-matched controls. For determination of PAI-1 plasma levels Frischmuth and colleagues used an enzyme immune assay (EIA) that detected PAI-1 in its active and latent form but not PAI-1 in complex with t-PA. In their analysis the authors found a dose dependent association between PAI-1 plasma levels and risk of VTE with an odds ratio (OR) of 1.73 for VTE in individuals within the highest tertile of PAI-1 levels compared to the lowest tertile. This dose response was also seen in all VTE subgroups studied by the authors, with similar ORs for the highest versus the lowest PAI-1 tertiles of 1.71 for VTE provoked by surgery, trauma, as acute MI, acute ischemic stroke, acute infection, immobilization, or active cancer at the time of VTE; 1.75 for unprovoked VTE; 1.75 for DVT; and 1.69 for PE.

Expectedly, the risk for VTE was almost doubled in obese individuals with a body mass index (BMI) ≥30kg/m^2 with an OR of 1.92 compared to those with a BMI <25kg/m^2. Interestingly however, when employing the Karlson-Holm-Breen method, the authors found that 15% of the association between obesity and VTE was accounted for by PAI-1.[16] This is of particular interest as there is ample evidence for a strong link between PAI-1 and obesity on the one hand and because obesity has been identified as a risk factor for VTE on the other hand.[17,18] Of note, obesity is also associated with a chronic inflammatory state and in the Tromsø Study as well as in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) trial the inflammatory marker C-reactive protein (CRP) was found to be responsible for 15 to 20% of VTE cases in obese individuals.[19,20] Frischmuth and colleagues, however, show in their paper that the VTE risk mediated by PAI-1 was independent of CRP levels thereby also ruling out confounding of their findings by other inflammatory mediators downstream to CRP such as interleukin-6, which has been shown to upregulate PAI-1 in adipose tissue.[21]

Based on their results, the authors speculate about targeting PAI-1 for therapeutic intervention to reduce the risk of VTE, in particular in obese individuals. The authors suggest that, as an alternative to direct PAI-1 inhibitors, which have been used in clinical trials but have not yet been approved for clinical use, mediators regulating the expression of PAI-1 such as components of the angiotensin system or hypoglycemic agents could be therapeutically targeted to reduce PAI-1 plasma levels in patients at risk.[22,23]

One of the strengths of this valuable study that should be emphasized is the fact that VTE patients were enrolled from a population-based cohort and the age- and sex-matched controls were selected from the same source population. Another asset of the study is the subgroup analysis performed by the authors who discriminated provoked from unprovoked VTE and analyzed cases of DVT and PE separately.

In summary, the authors succeeded in clearing the blurred picture surrounding a possible association of PAI-1 and VTE by showing for the first time a dose-dependent association of PA-1 with provoked and unprovoked VTE and a key role for PAI-1 in modulating the risk of VTE in obese patients. These findings could help establish PAI-1 not only as a predictive marker but also as a therapeutic target for VTE.

CONFLICTS OF INTEREST

There are no conflicts of interest reported by the author.

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How to cite this article: Wojta J. Commentary on "Elevated plasma levels of plasminogen activator inhibitor-1 are associated with risk of future incident venous thromboembolism": A new role for plasminogen activator inhibitor-1—An inhibitor of fibrinolysis predicts future venous thromboembolic events and links them to obesity. *J Thromb Haemost*. 2022;20:1559–1561. doi:10.1111/jth.15728