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Blood 142 (2023) 1266–1267

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

332.THROMBOSIS AND ANTICOAGULATION: CLINICAL AND EPIDEMIOLOGICAL

Association between Hereditary Angioedema and Venous Thromboembolism in a Large Population-Based Case-Control Study

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Introduction: Hereditary Angioedema (HAE) is a rare congenital disorder primarily caused by mutations in the *SERPING1* gene that results in C1 inhibitor (C1INH) deficiency or dysfunction. C1INH is a multifunctional serine protease inhibitor that functions as a major endogenous negative regulator of the kallikrein-kinin, contact pathway of coagulation and complement systems. HAE typically presents with episodes of unpredictable subcutaneous and submucosal swelling. However, HAE patients also have evidence of systemic activation of coagulation including elevated plasma prothrombin fragments, thrombin antithrombin complexes and D-dimers. Further, patients with HAE have recently been reported to have an increased risk of venous thromboembolism (VTE).
Methods: To evaluate the risk of VTE in patients with HAE we conducted a large population-based case-control study leveraging data from the United Kingdom Clinical Practice Research Datalink (CPRD). The CPRD Aurum dataset used here maintains anonymized electronic medical records of over 40 million individuals from over 1600 primary care practices in the United Kingdom. SNOMED CT medical codes were used to identify a cohort of 2,198 patients diagnosed with HAE between 1992 and 2022 in the CPRD Aurum dataset with a matched (age, gender, family practice, and index date for HAE) cohort of 4,376 controls selected. VTE events including deep vein thrombosis (DVT) and pulmonary embolism in the HAE case and control cohorts were identified using SNOMED CT medical codes. The Cox proportional hazards model was used to determine hazard ratios (HR) for VTE events in HAE cases versus controls adjusting for covariates age, sex, body mass index, blood pressure, smoking status and a number of co-morbidities specifically; neoplasm, type 2 diabetes, ischemic heart disease, chronic obstructive pulmonary disease, chronic kidney disease, autoimmune disorders and depression.
Results: A greater proportion of the HAE cases were female (62%) with a mean age at HAE diagnosis of 37 years. The median follow-up period for both cases and controls was 17 years (interquartile range (IQR):8-28 years). The overall incidence of VTE in HAE cases was 1.1/1000 patient years versus 0.6/1000 patient years in the control cohort. In unadjusted analyses HAE was associated with a significantly increased risk of VTE (HR 1.70, 95% CI 1.37-2.22, P<0.0001). Importantly, in adjusted analyses HAE remained significantly associated with an increased risk of VTE (HR 1.44, 95% CI 1.12-1.83, P=0.004, Figure 1). Of note, this association is similar in magnitude to that previously reported for heterozygous carriers of FV Leiden, the prothrombin gene mutation and high confidence loss of function mutations in Protein C and Protein S in comparable population-based case-control studies. In adjusted sub-analyses HAE was associated with a significantly increased risk of DVT (HR: 1.42, 95% CI 1.09-1.87, P=0.01) with a trend towards an increased risk of PE (HR 1.37, 95% CI 0.84-2.27, P=0.2).
Conclusions: The results of this population-based case-control study, roughly an order of magnitude larger in size than prior reports, demonstrate that HAE is associated with a significantly increased risk of VTE similar to that reported for common hereditary thrombophilias. These findings reinforce the important role of endogenous C1INH as a negative regulator of prothrombotic processes involved in VTE in the setting of HAE.

Disclosures Sundler Bjorkman: *CSL Behring:* Research Funding; *Biocryst:* Honoraria. **Bendapudi:** *Alexion Pharmaceuticals:* Consultancy; *Takeda Pharmaceuticals:* Consultancy. **Grover:** *CSL Behring:* Research Funding.

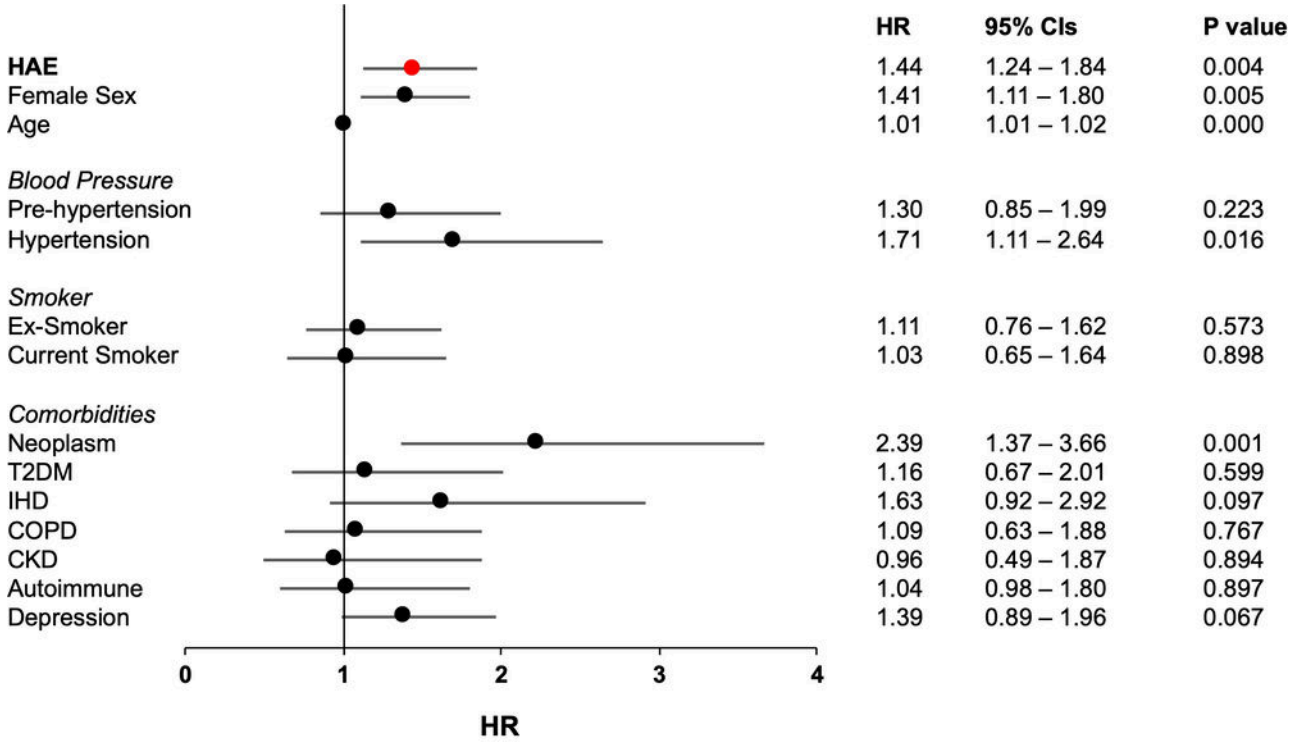

Figure: Association between HAE or select covariates and VTE
Forest plots representing the association between HAE or select covariates and VTE displayed as HRs with 95% CIs.

Figure 1

https://doi.org/10.1182/blood-2023-174693