C1-inhibitor levels and Venous Thromboembolism: Results from a Mendelian Randomization Study

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Hereditary angioedema is a rare condition, occurring once in 50 000-100 000.[1] It is characterized by recurrent swellings of cutaneous and submucosal tissue due to inadequate inhibition of bradykinin production caused by inherited C1-inhibitor deficiency. C1-inhibitor controls the complement, fibrinolytic, intrinsic coagulation, and contact systems by inhibition of several serine proteases including complement C1a, C1r, Mannan-binding lectin Serine Protease 1 (MASP-1), MASP-2, plasmin, kallikrein, and coagulation factors XIa and XIIa.[2] D-dimer levels may typically rise during angioedema attacks (presumably due to enhanced plasmin generation), but this increase during angioedema attacks is not associated with an increased thrombotic risk.[3] Several reviews on hereditary angioedema state that HAE, also outside the context of elevated D-dimer levels, is not associated with an enhanced risk of venous thromboembolism (VTE). However, no sources are available for this claim other than patients' and physicians' experience. However, a recent retrospective cohort study examining many potential comorbidities of hereditary angioedema with C1-inhibitor deficiency reported an association between hereditary angioedema and VTE.[4, 5] Notably, these findings could be confounded by indication and misclassification of VTE.[6] It is difficult to investigate this finding further with prospective cohort studies given the extreme rarity of hereditary angioedema. If HAE is indeed associated with VTE, one could postulate that less pronounced variations in C1-inhibitor levels could also be associated with VTE risk. Mendelian randomization (MR) is a suitable method to further investigate the potential causal association between C1-inhibitor levels and the potential risk for VTE. MR is a method that uses genetic variation as an instrument to assess the potential causal nature of an exposure and an outcome. The advantage of an MR approach is that it is much less affected by the risks of confounding and reverse causation that typically plague observational studies. A comprehensible overview of how Mendelian randomization works has been written by Davies et al.[7] In order to explore the causality between lower C1-inhibitor levels and venous thromboembolism, we performed a Mendelian randomization study.

We used data from publicly available GWAS. The studies used here received approval from their respective regulating bodies and all patients provided informed consent. For C1-inhibitor levels, we retrieved data from an aptamer-based protein GWAS in up to 35 559 Icelanders[8]. We selected the variants most strongly associated ($p < 5x10^{-8}$) with C1-inhibitor levels within 966 kbp around the gene (the ideal range according to Fauman and Hyde [9]), with a minor allele frequency > 0.05 and in low linkage ($R^2 < 0.01$). As clinical outcomes, we retrieved data on patients with venous thromboembolism based on ICD10 codes from the FinnGen[10] cohort (9 176 cases and 209 616 controls) and data on patients with self-reported deep venous thrombosis from the UK Biobank[11] (9 241 cases and 453 692 controls). We employed the inverse-variance weighted method as primary analysis and MR-egger, the weighted median and MR-PRESSO methods as sensitivity analyses. We used the TwoSampleMR package to perform the analyses.[12]

Per clinical outcome, eight common genetic variants associated with C1-inhibitor levels within 966 kbp around the gene and in low linkage disequilibrium were available for the analysis (explaining 9.0-9.3% of the difference in C1-inhibitor levels). In the main analyses, no association was found between genetically proxied C1-inhibitor levels and venous thromboembolism or deep venous thrombosis (FinnGen: OR 0.950, 95% CI 0.878;1.027, UK Biobank: OR 1.000, 95% CI 0.998;1.001). Sensitivity analyses did not show an association either (figure 1). There was no evidence for any heterogeneity (Finngen Cochran's Q P = 0.20, UK Biobank Cochran's Q P = 0.19) and MR-egger analyses did not show any evidence of pleiotropy (Finngen: P = 0.52, UK Biobank P = 0.20). MR-PRESSO did not identify any outlier genetic variants.

This Mendelian randomization study did not find evidence to support that genetically proxied C1-inhibitor levels are associated with venous thromboembolism. Our findings are indeed in contrast with a previous report that suggested a causal relation between reduced C1-inhibitor activity and venous thromboembolism.[5] This discrepancy could be attributable to confounding in the retrospective cohort study, since the association was not corrected for medication and could be confounded by misclassification[6]. To which extent treatment, e.g. chronic angioedema prophylaxis with antifibrinolytics or usage of indwelling central venous catheters for the administration of C1-inhibitor concentrates, increases the occurrence of venous thromboembolism in patients with hereditary angioedema remains to be explored. A retrospective survey among hereditary angioedema physicians estimated the frequency of an abnormal clotting event occurring in patients using C1-inhibitor concentrates with an indwelling catheter to be 18%.[13] Fortunately, given the recent advancements in prophylactic and on demand treatment options for hereditary angioedema,[14] usage of antifibrinolytics or indwelling central venous catheters are often no longer required nor recommended.[15] As with any MR study, there are limitations: first, we utilized common genetic variation with a relatively small and linear effect on C1-inhibitor levels. We cannot exclude that substantial C1-inhibitor deficiency as observed in hereditary angioedema could still have a significant effect on pathway homeostasis through the activation of positive feedback loops and therefor still be associated with increased VTE risk. Furthermore, due to the nature of MR, we could not take into account other risk factors for thrombosis that could be more prevalent in clinical HAE, like prolonged periods of incapacitation during attacks. Third, the lack of an association could simply be due to limited power. We sought to minimize this risk by utilizing data from the two largest publicly available GWAS. Ideally, large prospective cohort studies should establish the absence or presence of a true correlation between hereditary angioedema and venous thromboembolism. These studies should register concomitant medication usage and other risk factors for venous thromboembolism, should exclude angioedema attacks as the cause of thrombosis-mimicking symptoms such as abdominal pain or extremity swelling, and should confirm diagnoses of symptomatic venous thromboembolism with adequate imaging techniques. In the meantime, based on our Mendelian randomization analysis with common C1-esterase polymorphisms, we did not find evidence to suspect a causal relation between lower C1-esterase levels and venous

thromboembolism. Future prospective research should further explore the effects of lower and/or depleted C1-esterase levels and the risk for VTE.

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Addendum

The data used for this study is available in the public domain. The list of SNPs used for this study is available from the corresponding author upon request.

A.J. Cupido, R.S. Petersen, M. Levi, D.C. Cohn and L.M. Fijen contributed to the study conception. All authors contributed to the study design. A.J. Cupido performed the analyses. All authors interpreted the data. A.J. Cupido, R.S. Petersen and L.M. Fijen wrote the first draft of the manuscript and all authors commented on previous versions of the manuscript. All authors contributed to the article and approved the submitted version.

The authors declare no conflicts of interest.

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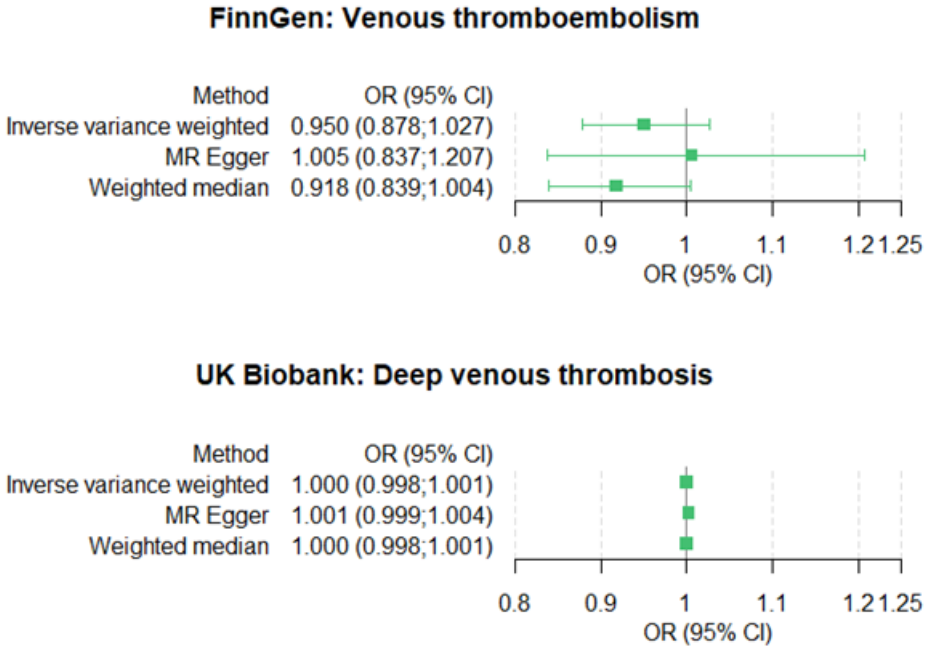
Figures/tables

Figure 1. Results from Mendelian randomization analyses



Legend: In primary and sensitivity analyses, no association was found between genetically proxied C1-inhibitor levels and venous thromboembolism or deep venous thrombosis.