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COMMENTARY

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Migraine and venous thrombosis: Another important piece of the puzzle

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In this issue of *Research and Practice in Thrombosis and Haemostasis* (*RPTH*), Folsom and colleagues report on the association between a migraine history and the risk of venous thromboembolism (VTE) in older adults.[1] For this purpose, the authors carried out an analysis on the well-known cohort study "The Atherosclerosis Risk in Communities (ARIC) Cohort," in which patients were interviewed from 1993 through 1995 regarding migraine, and followed for subsequent VTE through 2013. The analytic population comprised nearly 12 000 individuals, and the authors concluded that a migraine history was not associated with an increased risk of VTE (adjusted hazard ratio, 1.06; 95% confidence interval [CI], 0.82-1.36). While no association was observed between migraine without aura and VTE (adjusted hazard ratio, 0.97; 95% CI, 0.71-1.32), a weak association between migraine with aura and VTE could not be entirely ruled out (adjusted hazard ratio, 1.25; 95% CI, 0.85-1.85).

So how does this study add to the literature? It has been established previously that migraine is linked to an increased risk of ischemic stroke, ischemic heart disease, and atrial fibrillation, particularly among women and among migraine patients with aura.[2–5] Although the explanations for these associations are not fully understood, possible mechanisms involve endothelial dysfunction, hypercoagulability, platelet aggregation, vasospasm, presence of cardiovascular risk factors, paradoxical embolism, spreading depolarization, shared genetic risk, use of nonsteroidal anti-inflammatory drugs, and immobilization.[6–8] Some of these mechanisms may also contribute to the risk of other cardiovascular events. It should be noted that the magnitude of the increased cardiovascular risk associated with migraine observed in prior studies was fairly small at the absolute level, which is expected given the relatively young age of migraine patients, but it may translate into an increase in risk at the population level because migraine is a prevalent disease affecting around 1 billion people worldwide.[9] Most prior studies focused on the association between migraine and arterial cardiovascular events, and the analysis by Folsom et al extends the literature, providing evidence on the association with VTE. Interestingly, the findings by Folsom et al seem to be in contrast with previous reports.[4,10–12] One cohort study conducted in Denmark found an approximately 1.5-fold increased risk of VTE among patients with a hospital-based diagnosis of migraine with and without aura compared with an age- and sex-matched general population comparison cohort.[4] Another study from Taiwan of patients with migraine and a propensity-score matched comparison cohort of individuals without headache reported a 2.5-fold increased risk of VTE among migraine patients with aura, while the study found no association with VTE in migraine patients without aura.[11]

Why did the study by Folsom et al report findings in apparent contrast to previous studies? One potential explanation could be that there is no true causal association between migraine and VTE. Another explanation could be simply chance, combined with certain aspects of publication bias, that could have led to the publication of the first "positive" reports, which is now "corrected" by this "negative" publication. However, it is more plausible that the ostensibly contradictory findings may be inherent to the methodological details of the different studies, specifically the combination of differences in patient populations and migraine definitions, as well as varying follow-up periods.

One of the main strengths of the paper by Folsom et al was that data on migraine were of high quality, but, unfortunately, the number

of subjects with active and inactive migraine could not be distinguished. Clinically, migraine is characterized by recurrent headache episodes caused by increased excitability of the central nervous system with a peak in prevalence and incidence before the age of 50 years. Migraine is often ameliorated in older people, and thus it can be speculated that the analysis by Folsom et al included a large proportion of individuals with a history of migraine but without active migraine. If active migraine is in fact the exposure of interest, using the history of migraine as a proxy would lead to misclassification of the exposure and the measured effect would be diluted. In support of this notion, prior studies also suggested that the risk of VTE was particularly elevated in the short term following a migraine episode.[4]

Next to these insights on the association between migraine and venous thrombosis, there are 2 more general lessons to be learned. First, the paper nicely shows the added value of nonbinary thinking. When researchers look at their results and categorize them as being either "negative" or "positive" findings, a lot of information that underlies the results is lost. When relying solely on the practice of statistical testing, we lose information on the precision of the effect estimate as well as the potential impact of the associations.[13] *RPTH* and many other medical journals underwrite the STROBE statement, which clearly rejects the binary concept behind statistical testing in observational research and encourage authors to put emphasis on the precision of the point estimates of effect estimates.[14] This is exactly what the authors did when they concluded that "imprecision of our hazard ratios prevent firm conclusions about whether migraine might be a modest VTE risk factor." But the authors also discuss the relevance of weak risk factors with only a 20% increase in risk: "if migraine were (…) a weak risk factor, the association would be of little clinical (…) importance," which is correct, although the true clinical impact of associations should be interpreted in the light of absolute risks and other measures.[13] Nonetheless, this shows that "negative" findings, in particular those that provide a precise and valid answer to a research question, can have tremendous relevance to the field.

As a second general lesson, the paper by Folsom et al shows the importance of using extra analyses in order to increase the confidence of the findings, a process sometimes referred to as triangulation. It is the combined picture of the separate pieces that yields more confidence in the evidence than when the individual elements are assessed on their own. There are several ways the concept of triangulation can be translated to the field of epidemiologic research. One way to do the latter is by using so-called positive and negative controls. Often encountered in laboratory research, positive and negative control experiments help assess methodological validity as they respectively should or should not provide a certain result. For observational research, similar control analyses are not always possible, but when possible and well analyzed, the added value is often very high. Negative or positive controls in epidemiology often rely on the measurement of another exposure—one that should or should not be associated with the outcome of interest.[15] Folsom et al use a slightly different approach and substitute the main outcome with a proxy outcome. They show that migraineurs have no higher frequency of elevated hemostatic risk factors and genetic VTE risk score. In an argument on whether there is a relevant link between migraine and venous thrombosis risk, the strength of these results is modest at best, perhaps even weak, when presented on its own. But when combined with the other analysis, it adds another small piece of the puzzle, or line of evidence, in the words of Folsom et al., namely, that there does not seem to be a chronic effect of migraine on proxies of increased VTE risk.

It is this small but important piece of the puzzle that helps us to close the apparent gap between the paper by Folsom et al and previous publications. Folsom et al convincingly show that a history of migraine overall brings no relevant increase in long-term risk of venous thrombosis in an older population, while prior publications suggested primarily an acute relationship between the 2 common conditions. Therefore, even though these statements are at first in apparent juxtaposition, closer inspection of the paper by Folsom et al in the context of the current literature suggest that both pieces might still come from the same puzzle.

RELATIONSHIP DISCLOSURE

BS is member of the *RPTH* editorial board; BS and KA reviewed the initial submission as well as subsequent revisions.

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