Hacking stroke in women: towards aetiology-driven precision prevention

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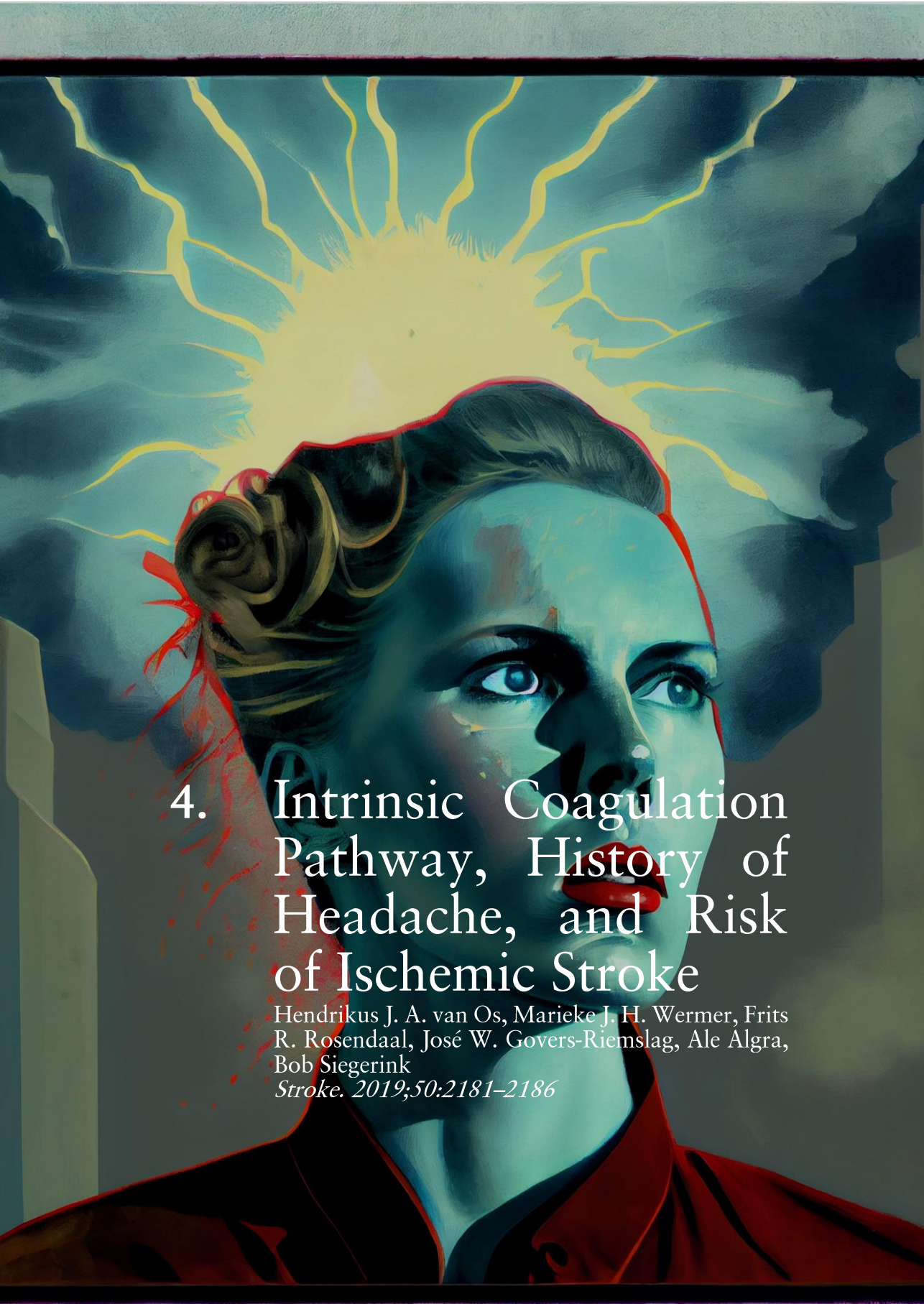

4. Intrinsic Coagulation Pathway, History of Headache, and Risk of Ischemic Stroke

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Abstract

Background and purpose: Hypercoagulable states in migraine patients may play a role in the pathophysiology underlying the association between migraine and ischemic stroke. This study aims to provide more insight into the potential association of headache, ischemic stroke and the intrinsic coagulation pathway.

Methods: We included patients from the RATIO study, a Dutch population-based case-control study including young women (age<50) with ischemic stroke and healthy controls. We defined a headache group based on a questionnaire on headache history. Intrinsic coagulation proteins were measured through both antigen levels (FXII, FXI, prekallikrein, HK) and protein activation, determined by measuring activated protein complex with C1esterase-inhibitor (FXIIa-C1-INH, FXIa-C1-INH, Kallikrein-C1-INH) or antitrypsin-inhibitor (FXIa-AT-INH). We calculated adjusted odds ratios (aOR), and performed an interaction analysis assessing the increase in stroke risk associated with high levels of intrinsic coagulation and history of headache.

Results: We included 113 ischemic stroke cases and 598 healthy controls. In total, 134 (19%) patients had a history of headache, of whom 38 were cases and 96 controls. The combination of headache and high intrinsic coagulation protein levels (all but FXII-antigen level and both FXIa-inhibitors) was associated with an increase in ischemic stroke risk higher than was expected based on their individual effects (aOR FXI antigen level alone: 1.7, 95%CI: 1.0–2.9, aOR headache alone: 2.0, 95%CI: 1.1–3.7, combination: 5.2, 95%CI: 2.3–11.6)

Conclusion: Headache and high intrinsic coagulation protein levels may biologically interact, increasing risk for ischemic stroke.

Introduction

Headache is a common symptom in the general population. Among women, migraine is one of the most common headache subtypes.[1] Migraine with aura (MA) is a cardiovascular risk factor and increases the risk of ischemic stroke approximately two-fold. This risk increase is most pronounced in young women, and is thought to be multicausal.[2-5] A likely contributing pathophysiological mechanism is hypercoagulability during or even between migraine attacks.[6-8] Several studies have shown platelet hyperactivity in migraine patients.[9-12] Additionally, multiple pro-thrombotic genetic polymorphisms have consistently been linked with migraine.[7, 13-17] Traditional thrombogenic factors such as von Willebrand factor (vWF), antiphospholipids (aPL) and prothrombin factor 1.2 were found to be elevated in migraine patients, though results were conflicting.[6, 18, 19] The proteins of the intrinsic coagulation pathway have not yet been assessed in headache patients in general and migraine patients in particular. The intrinsic coagulation proteins are linked to bradykinin formation (from the precursor High Molecular Weight Kininogen [HK]) and other related biological systems, which may play a role in the hemodynamic changes and vascular tone modifications observed during migraine attacks.[20-23] In acute ischemic stroke FXI plays a role in blood coagulation,[24] and high levels of activation of intrinsic coagulation proteins were found to increase stroke risk.[25-27]

This study aims to provide more insight into the connection between headache, ischemic stroke, and the intrinsic coagulation pathway in women. First, we will assess differences in intrinsic coagulation proteins between healthy controls with and without a history of headache, in a population of young women in whom we expect a high prevalence of migraine. Second, we will assess the interaction effect between history of headache and high levels of intrinsic coagulation proteins (activation and antigen levels) with respect to ischemic stroke risk.

Methods

Patients

We included patients from the Risk of Arterial Thrombosis In relation to Oral contraceptives (RATIO) study, a large multicenter population-based case-control study which included patients after the acute phase of their qualifying events that occurred between 1990 and 1995. The design of RATIO has been described previously.[25, 28-30] The aim of the RATIO study was to evaluate the risk of arterial thrombosis (both ischemic stroke and myocardial infarction) due to oral contraceptives of different generations. Inclusion criteria were age 18 to 50 years, no history of arterial thrombosis and confirmation of ischemic stroke by either

computed tomography or magnetic resonance imaging. Exclusion criteria were overt cardioembolic source of ischemic stroke, transient ischemic attack that lasted less than 24 hours, cerebral sinus venous thrombosis, carotid artery dissection, aphasia or cognitive impairment that prevented completion of the study questionnaire, or not speaking Dutch. Healthy controls were approached by random digit dialing and were frequency matched according to age, area of residence, and year of event. For the present study, we selected all ischemic stroke patients and all controls, based on whom we performed a complete case analysis with respect to both headache and intrinsic coagulation data. The RATIO study was approved by the ethics committees of the participating hospitals. All participants gave informed consent. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patient characteristics

Baseline data were collected via a standardized questionnaire on patient characteristics and self-reported cardiovascular risk factors, i.e. hypertension, diabetes mellitus, hypercholesterolemia, ethnicity, familial medical history, use of oral contraceptives, use of alcohol, and smoking habits. The RATIO study also included a short headache questionnaire with the following questions: 1. 'Did you suffer from headache prior to stroke (or prior to [index year] for controls)?' 2. 'Did you ever visit your general practitioner (GP) for headache?' 3. 'Did you ever visit a neurologist for the headache?' 4. 'Did the neurologist arrive at a diagnosis?' 5. 'Did the neurologist prescribe medication for the headache?' Since no specific migraine related questions were present, we constructed a proxy variable based on the questions on headache history. Participants were divided into a 'no headache' group (negative answer to questions 1 or 2), and a 'headache' group including possible migraine (positive answer to questions 1 and 2). Questionnaires elicited information from the time period preceding the year of ischemic stroke in cases, and the corresponding index year in controls

Intrinsic coagulation proteins

The measurement of the intrinsic coagulation proteins was performed around three months after ischemic stroke, and has been described in detail elsewhere.[25] In short, intrinsic coagulation activation was measured through protein-inhibitor complexes (FXIIa-C1-INH, FXIa-C1-INH, FXIa-AT-INH, KAL-C1-INH), and expressed as a proportion of fully activated normal pooled plasma. Antigen levels were measured by ELISA, and expressed as percentage of antigen levels in normal pooled plasma. In other publications of the RATIO study, high levels of intrinsic coagulation proteins were defined as coagulation activation or antigen levels higher than the 90th percentile cut-off point of the control group.[25, 29] Because of the restricted sample

size of our study population with respect to the total RATIO population, we applied the 75th percentile cut-off point for the definition of high levels of intrinsic coagulation protein antigen and activation.

Statistical analysis

Presence of individual high intrinsic coagulation levels and number of levels were assessed in healthy controls; ORs and corresponding 95% confidence intervals were estimated via logistic regression. We performed an analysis of additive interaction in a standard case-control comparison for all eight intrinsic coagulation protein and activation levels. We used logistic regression to estimate ORs and corresponding 95% confidence intervals as measures of relative risk for high level of the coagulation protein alone (-/+), for headache alone (+/-), and for both (+/+) in comparison with the reference category with neither (-/-) risk factor. All ORs from logistic regression models were adjusted for matching variables (age, region, and year of event), confounding was further minimized by adjusting all ORs for potential and known sources of confounding (hypercholesterolemia, alcohol use, contraceptive pill use, and smoking).

Results

The RATIO study included 203 cases with ischemic stroke and 925 controls. During the recruitment of the second phase of the study, 50 additional ischemic stroke cases were included. In total, 711 participants (60%) had complete intrinsic coagulation and headache data and were included in our study. Of these 711 participants 113 (16%) were ischemic stroke cases. The predefined headache group consisted of 134 participants (19%). (Figure)

Baseline characteristics of participants of this study showed that – as expected and earlier reported – traditional risk factors were more prevalent in ischemic stroke cases than controls, especially hypertension, contraceptive pill use and smoking.[25] (Table 1) Baseline characteristics of these 711 participants were similar to the characteristics of the total RATIO population. (Supplemental Table I)

Figure. Flowchart of participants included in this study

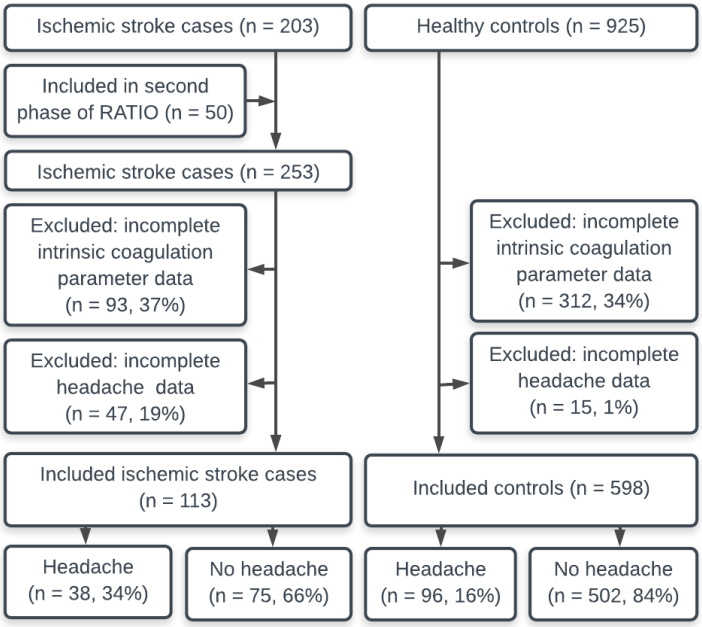

Table 1. Baseline characteristics of all participants

Baseline characteristics	Cases (n=113)	Controls (n=598)
Mean age (± SD)	40.5 (7.4)	38.9 (7.9)
Caucasian, n (%)	107 (96%)	569 (95%)
History, n (%)		
Hypertension	33 (29%)	38 (6%)
Diabetes mellitus	5 (4%)	10 (2%)
Hypercholesterolemia	7 (6%)	19 (3%)
Contraceptive pill use	54 (48%)	196 (33%)
Smoking	65 (58%)	252 (42%)
Alcohol use	67 (59%)	423 (71%)
History of headache, n (%)	38 (34%)	96 (16%)

Table 2. High levels of intrinsic coagulation proteins in healthy controls with and without a history of headache

Intrinsic coagulation protein†	Headache (n=96)	No headache (n=502)	OR (95% CI)*	aOR (95% CI)**
FXII antigen level	18 (19%)	134 (27%)	0.62 (0.36–1.08)	0.61 (0.35–1.07)
FXI antigen level	21 (22%)	130 (26%)	0.76 (0.44–1.30)	0.73 (0.42–1.36)
Prekallikrein antigen level	19 (20%)	131 (26%)	0.69 (0.40–1.19)	0.60 (0.34–1.05)
HK antigen level	24 (25%)	132 (26%)	0.96 (0.57–1.57)	0.83 (0.49–1.42)
FXIIa-C1-INH	24 (25%)	126 (25%)	0.88 (0.52–1.49)	0.76 (0.44–1.32)
FXIa-C1-INH	17 (18%)	132 (26%)	0.67 (0.37–1.20)	0.69 (0.38–1.24)
FXIa-AT-INH	19 (20%)	130 (26%)	0.80 (0.46–1.41)	0.82 (0.47–1.45)
KAL-C1-INH	14 (15%)	142 (28%)	0.47 (0.26–0.86)	0.47 (0.25–0.86)

**OR adjusted for matching variables (age, region, and year of event)'*

***OR adjusted for matching variables, hypercholesterolemia, contraceptive pill use, alcohol use and smoking*

Table 3. Ischemic stroke risk: interaction analysis of high intrinsic coagulation protein levels and activation, and headache

Intrinsic coagulation	>P75†	Headache	Controls, n (%)	Cases, n (%)	OR* (95% CI)	aOR** (95% CI)
FXII antigen level	-	-	368 (62%)	62 (55%)	1 (ref)	1 (ref)
	+	-	134 (22%)	13 (12%)	0.6 (0.3–1.1)	0.5 (0.2–0.9)
	-	+	78 (13%)	30 (27%)	2.0 (1.2–3.3)	1.9 (1.1–3.3)
	+	+	18 (3%)	8 (7%)	2.1 (0.8–5.3)	1.6 (0.6–4.3)
FXI antigen level	-	-	391 (65%)	45 (40%)	1 (ref)	1 (ref)
	+	-	111 (19%)	30 (27%)	1.8 (1.1–3.1)	1.7 (1.0–2.9)
	-	+	78 (13%)	21 (19%)	2.0 (1.1–3.7)	2.0 (1.1–3.7)
	+	+	18 (3%)	17 (15%)	5.7 (2.7–12.1)	5.2 (2.3–11.6)
Prekallikrein antigen level	-	-	371 (62%)	58 (51%)	1 (ref)	1 (ref)
	+	-	131 (22%)	17 (15%)	0.8 (0.4–1.4)	0.7 (0.4–1.3)
	-	+	77 (13%)	20 (18%)	1.4 (0.8–2.5)	1.4 (0.7–2.5)
	+	+	19 (3%)	18 (16%)	5.1 (2.4–10.6)	4.6 (2.1–10.1)
HK antigen level	-	-	370 (62%)	57 (50%)	1 (ref)	1 (ref)
	+	-	132 (22%)	18 (16%)	0.8 (0.5–1.5)	0.8 (0.5–1.5)
	-	+	72 (12%)	20 (18%)	1.6 (0.9–2.9)	1.5 (0.8–2.7)
	+	+	24 (4%)	18 (16%)	3.9 (1.9–7.9)	4.2 (2.0–8.9)
FXIIa-C1-INH	-	-	372 (62%)	53 (47%)	1 (ref)	1 (ref)
	+	-	130 (22%)	22 (20%)	0.9 (0.5–1.6)	0.9 (0.5–1.7)
	-	+	72 (12%)	24 (21%)	2.0 (1.1–3.5)	1.7 (1.0–3.1)
	+	+	24 (4%)	14 (12%)	2.8 (1.3–6.0)	3.6 (1.6–7.8)
FXIa-C1-INH	-	-	372 (62%)	49 (43%)	1 (ref)	1 (ref)
	+	-	130 (22%)	26 (23%)	2.2 (1.3–3.8)	2.2 (1.3–3.9)
	-	+	79 (13%)	29 (26%)	2.5 (1.5–4.4)	2.5 (1.4–4.3)
	+	+	17 (3%)	9 (8%)	4.5 (1.8–11.4)	4.4 (1.7–11.6)
FXIa-AT-INH	-	-	372 (62%)	47 (42%)	1 (ref)	1 (ref)
	+	-	130 (22%)	28 (25%)	2.2 (1.3–3.8)	2.1 (1.2–3.6)
	-	+	77 (13%)	32 (28%)	2.7 (1.6–4.6)	2.5 (1.5–4.4)
	+	+	19 (3%)	6 (5%)	4.0 (1.4–11.1)	4.2 (1.5–12.1)
KAL-C1-INH	-	-	360 (60%)	43 (38%)	1 (ref)	1 (ref)
	+	-	142 (24%)	32 (28%)	2.3 (1.3–3.8)	2.2 (1.3–3.8)
	-	+	82 (14%)	27 (24%)	2.3 (1.3–4.1)	2.3 (1.3–4.1)
	+	+	14 (2%)	11 (10%)	8.2 (3.3–20.5)	7.4 (2.9–19.1)

†Antigen or inhibiting factor level above 75th percentile
**OR adjusted for matching variables (age, region, and year of event)*
***OR adjusted for matching variables, hypercholesterolemia, alcohol use, contraceptive pill use, and smoking*

Second, we confirmed the association between the history of headache and ischemic stroke risk. Thirty eight stroke patients (34%) reported history of headache versus 96 women in the control group (16%), resulting in an aOR of 2.2 (95% CI: 1.4–3.6). (Supplemental Table II) Similar to history of headache, high levels of multiple intrinsic coagulation proteins were associated with an up to two-fold risk of ischemic stroke, which is in line with previous analyses of these data: FXI antigen (aOR 1.7, 95% CI: 1.0–2.9), FXIa-C1-INH (aOR: 2.2, 95% CI: 1.3–3.9), FXIa-AT-INH (aOR: 2.1, 95% CI: 1.2–3.6), and KAL-C1-INH (aOR: 2.2, 95% CI: 1.3–3.8). Interestingly, high FXII antigen levels were associated with a decrease in ischemic stroke risk (aOR: 0.5, 95% CI: 0.2–0.9), (Table 3) while previous analyses that applied the 90th percentile cut-off showed no association (aOR:1.0, 95% CI: 0.4–2.5).[29] The combination of both a history of headache and high intrinsic coagulation protein levels resulted in a clearly supra-additive stroke risk in five of eight intrinsic coagulation protein levels. This association was most pronounced for KAL-C1-INH (aOR protein alone: 2.2, 95% CI: 1.3–3.8, headache alone: 2.3, 95% CI: 1.3–4.1, combination: 7.4, 95% CI: 2.9–19.1), and FXI antigen level (aOR protein: 1.7, 95% CI: 1.0–2.9, aOR headache alone: 2.0, 95%CI: 1.1–3.7, combination: 5.2, 95% CI: 2.3–11.6. (Table 3) After additional adjustment for hypertension and diabetes the results of the interaction analysis remained essentially the same.

Discussion

In healthy controls we found that participants with a history of headache less often had high levels of KAL-C1-INH than those without a history of headache. For the combination of both risk factors (headache history and high intrinsic coagulation protein levels) we found an increase in ischemic stroke risk higher than could be expected based on individual effects of both factors. Other intrinsic coagulation protein antigen or activation levels were not associated with history of headache in healthy controls.

Our study shows synergistic effects of increased levels of the majority of all intrinsic coagulation proteins and positive headache history in increasing risk for ischemic stroke. These associations were most pronounced for KAL-C1-INH and FXI antigen, and may indicate a biological interaction between pathophysiological mechanisms underlying headache and the intrinsic hypercoagulability. These analyses further showed that the sole effect of the increased intrinsic coagulation levels and activation was largely in line with previous publications of the RATIO study.[25, 29] (Table 3) Especially high KAL-C1-INH and FXI antigen levels were strong risk factors for ischemic stroke, also in line with previous publications. FXII antigen showed a lower association with stroke risk than in previous publications,

possibly because we applied the 75th instead of the 90th percentile to define high levels of intrinsic coagulation proteins. Additionally, these analyses are restricted to those RATIO participants in whom headache data were complete. However, baseline variables of our subset were similar to those of the total RATIO population (see Supplemental Table I).[28, 29]

The increased ischemic stroke risk for patients with a history of headache and high intrinsic coagulation protein levels may be the result of a high migraine prevalence in the headache group. However, because we had no reliable data on migraine history this hypothesis remains speculative. Migraine, especially migraine with aura, has been found to be associated with endothelial dysfunction.[8, 31] Endothelial dysfunction causes a pro-thrombotic and pro-inflammatory state and impaired vascular reactivity, factors that could lead to clot initiation.[32, 33] Presence of high intrinsic coagulation antigen levels and activation could further lower the threshold for ischemic stroke in migraine patients by increased clot stability under flow, a process in which biological interaction with endothelial dysfunction mediated mechanisms could play a role.[34] Further, migraine has primarily been associated with platelet hyperactivity.[9-12] Activation of FXI by FXII can be bypassed in the coagulation cascade by feedback activation through thrombin as part of platelet-dependent arterial thrombosis.[35] Platelets contain a FXI receptor glycoprotein IBα, which stimulates this feedback activation in animal studies[36] and FXI-thrombin contributes to distal platelet activation and procoagulant microaggregate formation.[37] This may explain the relatively strong association of FXI activation and antigen levels compared with those of FXII.

Several methodological issues have to be considered. First and most important, because no migraine-specific questions were included in the headache questionnaire direct identification of patients with a history of migraine was not possible. History of headache can only to some extent be used as a proxy for migraine. Although sensitive (i.e. two-thirds of migraine patients visit the GP for their migraine specifically), the proxy has a low specificity.[38] Our study focusses on young women with a one-year migraine prevalence around 25%, making it safe to assume a substantial number of patients with headache in our study actually have migraine.[39] However, as exact prevalence and individual data on migraine are lacking, we cannot distinguish between migraine and non-migraine headache in our conclusions. An extensive literature search did not result in any studies investigating the association between tension or cluster headache and intrinsic or extrinsic coagulation parameters. Although we have no reason to suspect that such associations exist, we cannot rule out the possibility. For migraine the association with increased extrinsic coagulation parameters is well established. However, the hypothesis that migraine is the causative factor for any observed association

between history of headache and intrinsic coagulation proteins could not be assessed sufficiently with our data. The overall prevalence of history of headache in our population (19%) is lower than the average self-reported life-time prevalence of headache in the population (around 60%).[1] However, our definition of headache is more strict than self-reported headache, as it required a GP visit specifically for headache. A Dutch population study found that only 16% of patients with tension-type headache and around 25-50% of patients with migraine visit their GP specifically for headache complaints, explaining the headache prevalence of 19% in our controls.[40] This more restrictive definition likely results in a higher occurrence of moderate to severe headache phenotypes in our headache group including migraine. Second, as blood was collected after the event in the ischemic stroke group, reverse causation may have occurred. For this reason, we focused on the association between headache and intrinsic coagulation parameters only in the control group. In the interaction analysis however, we took the effect of intrinsic coagulation parameters on ischemic stroke risk into account, and also included ischemic stroke cases. Blood sampling in the RATIO study took place minimally one year and often 2-3 or more years after the event. Hence, we can rule out the possibility that our results directly reflect the transient effects of the acute phase of ischemic stroke, which lasts days to weeks. The absence of association between increased activation of the intrinsic coagulation proteins and myocardial infarction risk within the RATIO study suggests that a general post-hoc effect can also be ruled out. However, non-transient (or chronic) effects can still be the cause of reverse causation and can only be completely ruled out when blood samples are taken prior to the event.[25] Third, this study has no data on ischemic stroke sub-classification such as the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria.[41] Fourth, this study consists of young women only. Fourth, this study consists of young women only. This may decrease the generalizability of our results to men and to the elderly, although there are no plausible reasons why these associations would be qualitatively different in others. Fifth, we did not have direct data on anticoagulant use at time of blood drawing. We however could derive suspected oral anticoagulant use from endogenous thrombin potential data. The results of our analyses did not change when we excluded patients who were suspected to use oral anticoagulants at the time of blood drawing (data not shown). Finally, some analyses are based on a low number of participants, especially in the interaction analyses. This is reflected in the wide confidence intervals. So even when some results are 'statistically significant' in the traditional sense of $p < 0.05$, the imprecision of these estimates should be taken into account when interpreting our results. However, given the rare nature of ischemic stroke in young women, the number of included cases could be considered relatively large. Strong points of this study further include the detailed assessment of intrinsic coagulation parameters.

Our findings suggest that a biological interaction between history of headache and of intrinsic coagulation protein antigen levels and activation exists. We speculate that this interaction is caused by migraine although we were not able to investigate this in our study. Therefore, future studies in both men and women with detailed assessment of migraine are needed to assess the relationship of migraine and the intrinsic coagulation system. Especially investigation of the migraine with aura subset of migraine patients may be of interest, since in these patients the association with (micro)vascular abnormalities is better established. Additionally, good assessment of ischemic stroke subtype in such population could further elucidate the role of intrinsic coagulation proteins in the migraine-stroke relation.

References

1. Stovner L, Hagen K, Jensen R, Katsarava Z, Lipton R, Scher A, et al. The global burden of headache: A documentation of headache prevalence and disability worldwide. *Cephalalgia*. 2007;27:193-210
2. Kurth T, Gaziano JM, Cook NR, Logroscino G, Diener HC, Buring JE. Migraine and risk of cardiovascular disease in women. *JAMA*. 2006;296:283-291
3. Schurks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: Systematic review and meta-analysis. *BMJ*. 2009;339:b3914
4. Spector JT, Kahn SR, Jones MR, Jayakumar M, Dalal D, Nazarian S. Migraine headache and ischemic stroke risk: An updated meta-analysis. *Am. J. Med.* 2010;123:612-624
5. Stang PE, Carson AP, Rose KM, Mo J, Ephross SA, Shahar E, et al. Headache, cerebrovascular symptoms, and stroke: The atherosclerosis risk in communities study. *Neurology*. 2005;64:1573-1577
6. Hering-Hanit R, Friedman Z, Schlesinger I, Ellis M. Evidence for activation of the coagulation system in migraine with aura. *Cephalalgia*. 2001;21:137-139
7. Martinez-Sanchez P, Martinez-Martinez M, Fuentes B, Cuesta MV, Cuellar-Gamboa L, Idrovo-Freire L, et al. Migraine and hypercoagulable states in ischemic stroke. *Cephalalgia*. 2011;31:1609-1617
8. Tietjen GE. Migraine and ischaemic heart disease and stroke: Potential mechanisms and treatment implications. *Cephalalgia*. 2007;27:981-987
9. Allais G, D'Andrea G, Airola G, De Lorenzo C, Mana O, Benedetto C. Picotamide in migraine aura prevention: A pilot study. *Neurol. Sci.* 2004;25 Suppl 3:S267-269

10. Kitano A, Shimomura T, Takeshima T, Takahashi K. Increased 11-dehydrothromboxane b2 in migraine: Platelet hyperfunction in patients with migraine during headache-free period. *Headache*. 1994;34:515-518
11. Sarchielli P, Alberti A, Coppola F, Baldi A, Gallai B, Floridi A, et al. Platelet-activating factor (paf) in internal jugular venous blood of migraine without aura patients assessed during migraine attacks. *Cephalalgia*. 2004;24:623-630
12. Tomita H, Hatakeyama K, Soda W, Kobayashi T. Efficacy of ticlopidine for preventing migraine after transcatheter closure of atrial septal defect with amplatzer septal occluder: A case report. *J. Cardiol.* 2007;49:357-360
13. Pezzini A, Grassi M, Del Zotto E, Giossi A, Monastero R, Dalla Volta G, et al. Migraine mediates the influence of c677t mthfr genotypes on ischemic stroke risk with a stroke-subtype effect. *Stroke*. 2007;38:3145-3151
14. Pezzini A, Grassi M, Lodigiani C, Patella R, Gandolfo C, Casoni F, et al. Predictors of migraine subtypes in young adults with ischemic stroke: The italian project on stroke in young adults. *Stroke*. 2011;42:17-21
15. Yasui K, Kowa H, Nakaso K, Takeshima T, Nakashima K. Plasma homocysteine and mthfr c677t genotype in levodopa-treated patients with pd. *Neurology*. 2000;55:437-440
16. Kutai M, Raviv R, Levin C, Hugeirat Y, Shalev S, Zalman L, et al. Migraine and hypercoagulability, are they related? A clinical study of thrombophilia in children with migraine. *Br. J. Haematol.* 2011;152:349-351
17. Maitrot-Mantelet L, Horellou MH, Massiou H, Conard J, Gompel A, Plu-Bureau G. Should women suffering from migraine with aura be screened for biological thrombophilia?: Results from a cross-sectional french study. *Thromb. Res.* 2014;133:714-718
18. Cavestro C, Mandrino S. Thrombophilic disorders in migraine. *Front. Neurol.* 2014;5:120
19. Tietjen GE, Khubchandani J, Herial N, Palm-Meinders IH, Koppen H, Terwindt GM, et al. Migraine and vascular disease biomarkers: A population-based case-control study. *Cephalalgia*. 2018;38:511-518
20. Colman RW, Schmaier AH. Contact system: A vascular biology modulator with anticoagulant, profibrinolytic, antiadhesive, and proinflammatory attributes. *Blood*. 1997;90:3819-3843
21. Gallai V, Sarchielli P, Firenze C, Trequattrini A, Paciaroni M, Usai F, et al. Endothelin 1 in migraine and tension-type headache. *Acta Neurol. Scand.* 1994;89:47-55
22. Kaplan AP, Ghebrehiwet B, Silverberg M, Sealey JE. The intrinsic coagulation-kinin pathway, complement cascades, plasma renin-angiotensin system, and their interrelationships. *Crit. Rev. Immunol.* 1981;3:75-93

23. Schmaier AH. Assembly, activation, and physiologic influence of the plasma kallikrein/kinin system. *Int. Immunopharmacol.* 2008;8:161-165
24. Goldman S, Prior SM, Bembenek JP, Niewada M, Broniatowska E, Czlonkowska A, et al. Activation of blood coagulation and thrombin generation in acute ischemic stroke treated with rtpa. *J. Thromb. Thrombolysis.* 2017;44:362-370
25. Siegerink B, Govers-Riemslag JW, Rosendaal FR, Ten Cate H, Algra A. Intrinsic coagulation activation and the risk of arterial thrombosis in young women: Results from the risk of arterial thrombosis in relation to oral contraceptives (ratio) case-control study. *Circulation.* 2010;122:1854-1861
26. Schmaier AH. The contact activation and kallikrein/kinin systems: Pathophysiologic and physiologic activities. *J. Thromb. Haemost.* 2016;14:28-39
27. van Montfoort ML, Meijers JC. Recent insights into the role of the contact pathway in thrombo-inflammatory disorders. *Hematology Am. Soc. Hematol. Educ. Program.* 2014;2014:60-65
28. Siegerink B, Rosendaal FR, Algra A. High-molecular-weight kininogen and the risk of a myocardial infarction and ischemic stroke in young women: The ratio case-control study. *J. Thromb. Haemost.* 2012;10:2409-2412
29. Siegerink B, Rosendaal FR, Algra A. Antigen levels of coagulation factor xii, coagulation factor xi and prekallikrein, and the risk of myocardial infarction and ischemic stroke in young women. *J. Thromb. Haemost.* 2014;12:606-613
30. Urbanus RT, Siegerink B, Roest M, Rosendaal FR, de Groot PG, Algra A. Antiphospholipid antibodies and risk of myocardial infarction and ischaemic stroke in young women in the ratio study: A case-control study. *Lancet Neurol.* 2009;8:998-1005
31. Tietjen GE. Migraine as a systemic vasculopathy. *Cephalalgia.* 2009;29:987-996
32. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: A marker of atherosclerotic risk. *Arterioscler. Thromb. Vasc. Biol.* 2003;23:168-175
33. Widlansky ME, Gokce N, Keaney JF, Jr., Vita JA. The clinical implications of endothelial dysfunction. *J. Am. Coll. Cardiol.* 2003;42:1149-1160
34. Kuijpers MJ, van der Meijden PE, Feijge MA, Mattheij NJ, May F, Govers-Riemslag J, et al. Factor xii regulates the pathological process of thrombus formation on ruptured plaques. *Arterioscler. Thromb. Vasc. Biol.* 2014;34:1674-1680
35. Fogelson AL, Hussain YH, Leiderman K. Blood clot formation under flow: The importance of factor xi depends strongly on platelet count. *Biophys. J.* 2012;102:10-18

36. Kossmann S, Lagrange J, Jackel S, Jurk K, Ehlken M, Schonfelder T, et al. Platelet-localized fxi promotes a vascular coagulation-inflammatory circuit in arterial hypertension. *Sci. Transl. Med.* 2017;9
37. Zilberman-Rudenko J, Itakura A, Wiesenekker CP, Vetter R, Maas C, Gailani D, et al. Coagulation factor xi promotes distal platelet activation and single platelet consumption in the bloodstream under shear flow. *Arterioscler. Thromb. Vasc. Biol.* 2016;36:510-517
38. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the united states: Data from the american migraine study ii. *Headache*. 2001;41:646-657
39. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF, et al. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology*. 2007;68:343-349
40. Knuistingh neven a, couturier egm. Diagnostiek van chronisch-recidiverende hoofdpijn. Tijdschr huisartsgeneeskd 2003;20:174-8.
41. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. Toast. Trial of org 10172 in acute stroke treatment. *Stroke*. 1993;24:35-41