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New insights in the risk profile for arterial thrombosis : differences and similarities in risk factors between myocardial infarction and ischaemic stroke

Maino, A.

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Author: Maino, Alberto
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Chapter 6

Concomitant headache influences long-term prognosis after acute cerebral ischaemia of non-cardioembolic origin

Alberto Maino, Ale Algra,Peter J. Koudstaal, Erik W. van Zwet, Michel D. Ferrari, Marieke J.H. Wermer, on behalf of the LiLAC Study Group

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Abstract

Background and Purpose: Acute cerebral ischaemia is frequently associated with headache. It is unknown whether concomitant headache reflects a partly different pathogenesis and thus may influence long-term prognosis after stroke. Here we compared the long-term risk of recurrent vascular events in patients in whom a transient ischaemic attack (TIA) or minor ischaemic stroke of non-cardioembolic origin was associated with headache with those without headache.

Methods: We used data from the LiLAC (Life Long After Cerebral ischaemia) cohort. Participants were grouped based on the presence or absence of headache at presentation. We calculated the hazard ratios (HRs) and corresponding 95% confidence intervals (CI) for any first vascular event (primary outcome) or any cardiac or cerebral event (secondary outcomes). Adjustments were made for baseline clinical characteristics.

Results: Of 2473 participants, 420 (17%) experienced headache during the acute event. Median follow-up was 14.1 years. For the primary outcome, the crude HR of headache vs. no headache was 0.75 (95% CI 0.66-0.89) and the adjusted HR 0.83 (95% CI 0.71-0.97). For cardiac events the adjusted HR was 0.88 (95% CI 0.67-1.14) and for cerebral events, 0.97 (95% CI 0.76-1.24). The ratio of cardiac versus cerebral events, however, did not differ between the two groups. Participants with headache were at lower risk of vascular death (adjusted HR 0.73; 95% CI 0.61-0.87).

Conclusions: Patients who experienced headache in association with a TIA or minor ischaemic stroke have a better vascular prognosis than those without concomitant headache. This may, at least partly, reflect a different pathogenesis.

Introduction

Ischaemic strokes are associated with headache in over a quarter of cases.[1-5] This might be due to stimulation of sensory afferents of the trigeminovascular system, either directly by ischaemia or indirectly by cortical spreading depression (SD) secondary to cerebral ischaemia.[6-8] In rare cases, headache may reflect migrainous stroke.[9, 10] Alternatively, it has been estimated that up to 30% of patients with a presumed transient ischaemic attack (TIA) in fact had a migraine attack with headache and neurological aura symptoms.[11-13] It is thus conceivable that distinct pathophysiological mechanisms are, at least partly, involved in cerebral ischaemic events with and without associated headache. If true, there might also be a different prognosis for recurring vascular events.[14] Here we compared, in a large cohort of patients with established TIA or minor ischaemic stroke, the long-term risk of recurrent vascular events in patients with and without associated headache.

Methods

Patients and study design

For this study we used data of 2473 participants who were included in the LiLAC (Life Long After Cerebral ischaemia) cohort, which is based on the Dutch TIA Trial (DTT) that started in 1986. The background, design, and results of this multicenter trial have been described in detail elsewhere.[15] In brief, participants with a TIA (symptoms for less than 24 hours) or minor ischaemic stroke (symptoms for more than 24 hours) and who were still independent in most daily activities (modified Rankin scale <= 3), were, within three months from onset, randomly assigned to 30 mg or 283 mg of aspirin, or 50 mg of atenolol or its placebo, in a factorial design. Participants with a cardiac source of embolism or a clotting disorder were excluded. In the LiLAC study, follow-up of all the participants who were still alive at the end of the DTT (spring 1990) was extended up to the period between March 2001 and December 2003.[16] For logistical reasons only patients from the 24 hospitals which had enrolled at least 50 patients in the DTT were included in LiLAC (2473 of the original 3150). Follow-up data were obtained from the neurologists who had included patients in the DTT and the patients' general practitioner. If data were still incomplete, the participant (or, if unavailable, a relative or acquaintance) was contacted directly. All the participants were informed about the background and procedures of the trial, both through discussion and by means of a printed information sheet, and all gave their explicit consent. The protocol of the LiLAC study was approved by the ethics committee of the University Medical Centre Utrecht.

Baseline characteristics

Extensive baseline characteristics were recorded in the DTT by neurologists using a checklist that was specifically worded to be understood by patients. The list contained several multiple-choice questions about the nature and time course of symptoms, including the presence and onset of any kind of headache, and whether the headache was throbbing or continuous. Because the primary aim of the DTT was to assess treatment effects of aspirin and atenolol, no other headache details, nor the presence of associated (migraine) symptoms were recorded. Headache was taken as any headache reported by the patient occurring simultaneous with the onset of TIA or minor stroke.[17] Apart from the specific history, records included demographic data, vascular risk factors, vascular history, blood pressure, physical examination, laboratory tests, electrocardiogram (ECG), and medications. A brain CT scan was obtained in all participants, apart from those with only transient monocular blindness. Cerebral infarcts were defined as circumscribed hypodense lesions and subdivided into lacunar small deep lesions and cortical infarcts. Infarcts were further subdivided according to their location. Depending on the clinical details, the scans were classified as showing relevant infarcts (lesions concordant with the symptoms) or irrelevant infarcts (lesions not concordant with the symptoms).

Outcome event

Our primary outcome measure was the composite event of death from all vascular causes, non-fatal stroke (caused by ischaemia or haemorrhage) or non-fatal myocardial infarction, whichever occurred first. Separate analyses were performed for the outcomes cardiac events (fatal or non-fatal myocardial infarction, death from congestive heart failure and sudden death), cerebral events (fatal or non-fatal ischaemic or haemorrhagic stroke) and deaths. Deaths were furthermore classified as vascular or non-vascular deaths. The definition of vascular death included sudden death (unexpected cardiac death within an hour of onset of symptoms, or within 24 hours if the patient was unexpectedly found dead), or death from stroke, myocardial infarction, congestive heart failure, or systemic bleeding. All events were classified independently by three physicians specialized in the field of cerebrovascular disease according to criteria described previously.[16]

Statistical analysis

Median follow-up was calculated using the estimates of the censoring distribution as described previously.[18] The occurrence of outcome events in patients with onset headache and those without onset headache was compared in terms of hazard ratios (HRs). HRs were determined with the cause-specific Cox proportional hazards model, with corresponding 95% confidence intervals (CI), and adjusted in bivariable analyses for differences in baseline characteristics between patients with or without headache. A final multivariable model was built, which included all variables that changed the crude HR by at least 5% in the bi-variable analyses. Pre-specified subgroups analyses were performed for the primary outcome, and a forest plot of adjusted HRs was drawn. For a visual comparison of the two groups, nonparametric cumulative incidence functions were drawn.[19] They are a crude representation of the data and show the competing risks of death, cardiovascular and cerebral event over time. Cumulative incidence ratios (CIRs) of cardiac events to cerebral events were calculated from these functions with corresponding bootstrap 95% CI. Differences in CIRs between the two groups were tested at various times (5, 10 and 15 years of follow-up) by means of a permutation test. Significance level was set at $p<0.05$.

Table 1. Baseline characteristics of the 2473 patients included in the study.

Characteristics	**headache** N=420	**no headache** N=2053
Demographics		
Age (years; SD)	63.3 (10.5)	65.6 (10)
Male	258 (61%)	1350 (66%)
History		
Myocardial infarction	54 (13%)	205 (10%)
Intermittent claudication	22 (5%)	106 (5%)
Diabetes mellitus	28 (7%)	174 (8%)
Hypertension	151 (36%)	889 (43%)
Angina	56 (13%)	198 (10%)
Hyperlipidaemia	17 (4%)	77 (4%)
Smoking	181 (43%)	944 (46%)
Event		
Minor ischaemic stroke	314 (75%)	1400 (68%)
TIA	106 (25%)	653 (32%)
Rankin grade >=2	106 (25%)	466 (23%)
Visual disturbances only	23 (5%)	139 (7%)
Pure motor symptoms	159 (38%)	866 (42%)
Pure sensory symptoms	24 (6%)	103 (5%)
Sensory-motor symptoms	136 (32%)	668(33%)
Dizziness	77 (18%)	184 (9%)
Paresis	276 (66%)	1487 (73%)
Dysarthria	94 (22%)	494 (24%)
Aphasia	79 (19%)	400 (20%)
Lacunar syndrome	188 (45%)	1182 (58%)
Vertebrobasilar syndrome	70 (17%)	212 (10%)
12 lead ECG		
Q wave	56 (13%)	299 (15%)
ST-depression	36 (9%)	175 (9%)
Negative T wave	52 (12%)	197 (10%)
Acute phase hypertension		
Systolic blood pressure > 160 mmHg	184 (44%)	1077 (52%)
Diastolic blood pressure > 90 mmHg	254 (60%)	1297 (63%)

Results

Headache was recorded in 420/2473 (17%) participants. Baseline characteristics and CT findings of the headache and non-headache groups are summarized in Tables 1 and 2. Follow-up was complete for all participants until close-out of the DTT. After that, 26 patients were lost to follow-up.

Table 2. CT characteristics at the time of the initial TIA or minor stroke.

CT findings (N=2362)	**headache** N=404	**no headache** N=1958
Any infarct	165 (41%)	820 (42%)
Irrelevant infarct only	33 (8%)	198 (10%)
Relevant infarct	132 (33%)	622 (32%)
Type and location of relevant infarct		
Anterior circulation	66 (50%)	462 (74%)
Posterior circulation	51 (39%)	90 (14%)
Cortical infarcts	51 (39%)	145 (23%)
Lacunar infarcts	40 (30%)	367 (59%)

CT, computer tomography.

The overall median follow-up was 14.1 years (IQR 13.1 - 15.1). The crude hazard ratio for vascular events for patients with headache as compared with those without headache was 0.75 (95% CI 0.66-0.89). After multivariable adjustment for all relevant variables the HR slightly increased to 0.83 (95% CI 0.71-0.97) (Table 3).

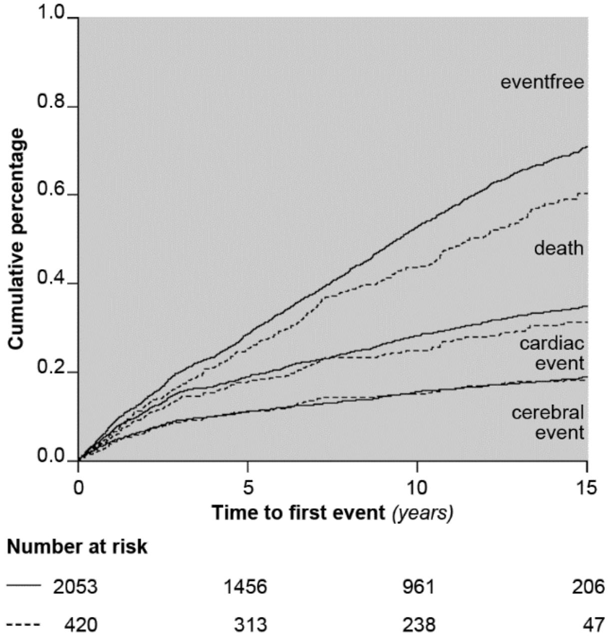
Table 3. Crude and adjusted hazard ratios for long-term vascular events.

Outcome event	Headache N=420	No headache N=2053	Crude HR (95% CI)	Adjusted HR (95% CI)[1]
First vascular event	196 (47%)	1144 (56%)	0.75 (0.66 - 0.89)	0.83 (0.71 - 0.97)
Cerebral event (fatal and non-fatal)	79 (19%)	395 (19%)	0.91 (0.72 - 1.16)	0.97 (0.76 - 1.24)
Cardiac event (fatal and non-fatal)	66 (16%)	364 (18%)	0.81 (0.63 - 1.06)	0.88 (0.67 - 1.14)
Death	210 (50%)	1279 (62%)	0.72 (0.62 - 0.83)	0.78 (0.68 - 0.91)
Vascular death	140 (33%)	936 (45%)	0.66 (0.55 - 0.79)	0.73 (0.61 - 0.87)
Non-vascular death	70 (17%)	343 (17%)	0.89 (0.69 - 1.15)	0.93 (0.72 - 1.21)

[1] *HRs are adjusted for age, sex, history of hypertension, history of angina, Modified Rankin Score (MRS), negative T wave on ECG and lacunar syndrome at presentation.*

Patients with headache tended to have a slightly reduced risk of fatal or non-fatal myocardial infarction (adjusted HR 0.88; 95% CI 0.67-1.14). No difference between the two groups was found in the risk of fatal or non-fatal stroke (adjusted HR 0.97; 95% CI 0.76-1.24). Patients with headache had a lower risk of death from vascular events than those without headache (adjusted HR 0.73; 95% CI 0.61-0.87), whereas no difference was found in the risk of non-vascular death.

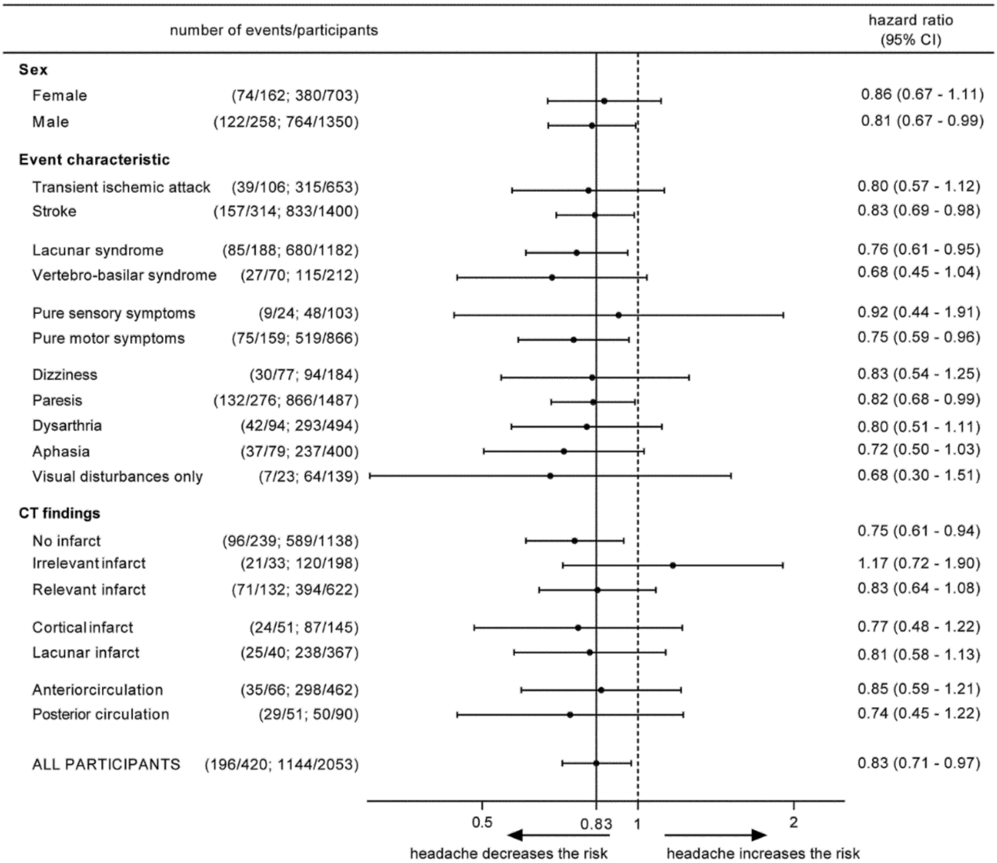
Figure 1. Non parametric cumulative incidence functions for cardiac events (fatal and non-fatal myocardial infarction), cerebral events (fatal and non-fatal ischaemic stroke) and death.



Solid and dashed lines represent participants without headache and with headache respectively.

The non-parametric cumulative incidence curves in Figure 1 illustrate the crude cumulative percentages of patients with and without headache who had a cardiac event or a recurrent cerebral event. At 5, 10 and 15 years of follow-up the cumulative incidence ratios of cardiac events to cerebral events were respectively 0.62 (95% CI 0.35-0.96), 0.64 (95% CI 0.41-0.94), 0.71 (95% CI 0.47-0.99) for the headache group and 0.70 (95% CI 0.57-0.86), 0.81 (95% CI 0.69-0.96), 0.84 (95% CI 0.73-0.97) for the no headache group. Cumulative incidence ratios did not differ significantly between the two groups at any time period (at 5, 10 and 15 years p=0.60; p=0.25; p=0.35, respectively).

Figure 2. Forest plot of hazard ratios and 95% confidence intervals for first vascular events by subgroups.



Numbers between parentheses indicate: number of patients with headache who experienced the event/total number of patients at risk; number of patients without headache who experienced the event/total number of patients at risk. Hazard ratios are adjusted for age, sex, history of angina, history of hypertension, modified Rankin Scale, negative T wave on ECG and lacunar syndrome at presentation. Horizontal line represents 95% confidence limits. Solid vertical line represents the overall adjusted hazard ratio for first vascular event in the entire population.

In a separate analysis, we assessed which of the demographic or clinical characteristics implied a particularly reduced risk of vascular events. Patients presenting with headache and vertebro-basilar syndrome (HR 0.68; 95% CI 0.45-1.04), aphasia (HR 0.72; 95% CI 0.50-1.03) or visual disturbances only (HR 0.68; 95% CI 0.30-1.51) were found to have the lowest risk (Figure 2), but hazard ratios did not differ in a statistically significant way between subgroups.

Discussion

We found that participants in whom a TIA or minor ischaemic stroke was associated with headache had a reduced long-term risk of recurrent vascular events compared with those without headache. This effect seems mainly due to a reduced risk of vascular death. Besides the lower risk of vascular death, our results also suggested a lower risk of cardiac events in participants with headache, whereas the risk of cerebral events seemed comparable to participants without headache. This different trend in cardiac events opposed to cerebral events, however, was not statistically significant.

Our study is the first comparing the long-term vascular prognosis of ischaemic stroke with and without concomitant headache. Onset headache was present in 17% of our population, more frequent among women, and more often associated with lesions involving the cortical and posterior circulation, as reported in other studies.[17, 20] Previous studies that focused on short-term outcome found no relationship between concomitant headache and stroke severity, in hospital mortality and 6 months outcome.[21, 22] The long duration of follow-up, the large number of participants and the large number of outcome events enabled us to adjust for several covariates. The hazard ratio for first vascular event remained statistically significant after adjustment for potential confounders.

The present study also has limitations. Detailed headache profiles, such as history of migraine, severity or location, were not recorded. Therefore we could not relate these characteristics to the outcomes. In addition, the selection of participants was restricted to non-cardio embolic TIA or minor stroke. The exclusion of large infarcts reduces the bias related to survival in the acute phase but could also limit the generalizability of the findings.

The Dutch TIA Trial was performed before the TOAST criteria were published, and no formal classification of stroke source was recorded. In the trial, patients with cerebral ischaemia due to identifiable causes other than arterial thrombosis or arterial embolism, including atrial fibrillation, were excluded and therefore, the participants of our study have cerebral ischaemia of *presumed* arterial origin. We cannot exclude, however, that some of our participants had a cryptogenic source of stroke which in some studies is related to a different outcome than other subtypes of stroke.[23, 24]

It is unlikely that the lower vascular event rate in the participants with headache is caused by a higher number of TIA mimics in this group, because there were no differences in hazard ratios between participants presenting with a TIA or a minor ischaemic stroke and participants with or without ischaemic lesions on the CT scan (Figure 2).[13, 25]

The more benign long-term vascular prognosis in patients with headache points to a possible different pathophysiology of the presenting TIA or minor stroke. Certain subtypes of stroke, including arterial dissections and the reversible cerebral vasoconstriction syndrome (RCVS), present more often with headache than others and are also associated with better long term prognosis after the event. [23, 26] Although arterial dissection and RCVS are relative rare causes of ischaemic stroke, we cannot exclude that they have played a role in our results.

It has been proposed that headache related to stroke is due to stimulation of sensory afferents of the trigeminovascular system.[8] The stimulation could be either directly by ischaemia or indirectly by factors associated with ischaemia. One factor that might play a role in the indirect stimulation of the trigeminovascular system is cortical spreading depression (SD).[7] SD is the likely mechanism for migraine aura and is characterized by slowly spreading waves of neuronal depolarization and associated changes in cerebral blood flow.[27] SD is related to stroke in different ways. First, it may increase susceptibility to stroke. Transgenic mice harboring the human familial hemiplegic migraine type 1 *CACNA1A* calcium channel gene mutation are highly susceptible to SD and have increased sensitivity to ischaemia, predisposing them to strokes during mild ischaemic events.[28, 29] Second, SD was found in the penumbra of non migrainous patients with middle cerebral artery infarction increasing the infarct lesion size.[30] It is unknown whether the occurrence of SD depends on subtype or cause of stroke and whether this has influence on the long-term prognosis of stroke patients.[31] Headache could be a marker of the presence of SD, even in patients without a history of migraine.

Blood pressure is another factor that is involved in the pathophysiology of stroke related headache. It was previously reported that one of the independent predictors of headache in patients with stroke is the absence of a history of hypertension.[32] This was also confirmed in our cohort and could suggest that atherosclerosis plays a less important role in the pathogenesis of stroke with headache.

We hypothesize that ischaemic stroke with concomitant headache reflects a different subtype of stroke compared to stroke related to other mechanisms, such as atherosclerosis. Future studies are required to confirm this.

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