Concomitant Headache Influences Long-term Prognosis After Acute Cerebral Ischemia of Noncardioembolic Origin

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

Background and Purpose—Acute cerebral ischemia 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 ischemic attack or minor ischemic stroke of noncardioembolic origin was associated with headache with those without headache.

Methods—We used data from the Life Long After Cerebral ischemia (LiLAC) cohort. Participants were grouped on the basis of 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 versus 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 2 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 transient ischemic attack or minor ischemic stroke have a better vascular prognosis than those without concomitant headache. This may, at least partly, reflect a different pathogenesis. (Stroke. 2013;44:2446-2450.)

Key Words: cohort studies | headache | headache disorders, secondary | prognosis | stroke

Ischemic strokes are associated with headache in more than a quarter of cases.1-5 This might be because of stimulation of sensory afferents of the trigeminovascular system, either directly by ischemia or indirectly by cortical spreading depression (SD) secondary to cerebral ischemia.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 ischemic 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 ischemic 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 ischemic stroke, the long-term risk of recurrent vascular events in patients with and without associated headache.

Patients and Methods

Patients and Study Design
For this study, we used data of 2473 participants who were included in the Life Long After Cerebral ischemia (LiLAC) cohort, which is on the basis of 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 <24 hours) or minor ischemic stroke (symptoms for >24 hours) and who were still independent in most daily activities (modified Rankin scale ≤3) were, within 3 months from onset, randomly assigned to 30 mg or 283 mg of aspirin, or 50 mg of atenolol and 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 the LiLAC (2473 of the original 3150). Follow-up data were obtained from the neurologists who had included patients in the DTT and from their general practitioners.

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From the Unit of Internal Medicine 2, Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione IRCCS Ca’ Granda - Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy (A.M.); Departments of Clinical Epidemiology (A.M., A.A.), Biostatistics (E.W.v.Z.), and Neurology (M.D.F., M.J.H.W.), Leiden University Medical Center, Leiden, The Netherlands; UMC Utrecht Stroke Center, Department of Neurology and Neurosurgery (A.A.) and Julius Centre for Health Sciences and Primary Care (A.A.), University Medical Center, Utrecht, The Netherlands; and Department of Neurology, Erasmus Medical Center, Rotterdam, The Netherlands (P.J.K.).


Correspondence to Ale Algra, MD, PhD, Department of Neurology and Julius Center, UMC Utrecht, PO Box 85500, Mailbox STR 6.131, Room STR 7.140, 3508 GA Utrecht, The Netherlands, E-mail a.algra@umcutrecht.nl

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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 Center 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. Apart from the specific history, records included demographic data, vascular risk factors, vascular history, blood pressure, physical examination, laboratory tests, ECG, and medications. A brain computed tomographic (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, nonfatal stroke (caused by ischemia or hemorrhage), or nonfatal myocardial infarction, whichever occurred first. Separate analyses were performed for the outcomes cardiac events (fatal or nonfatal myocardial infarction, death from congestive heart failure, and sudden death), cerebral events (fatal, nonfatal ischemic, or hemorrhagic stroke), and deaths.

### Statistical Analysis

Median follow-up was calculated using the estimates of the censoring distribution as described previously. 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 bivariable analyses.

### Results

Headache was recorded in 420/2473 (17%) participants. Baseline characteristics and CT findings of the headache and nonheadache 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.

The overall median follow-up was 14.1 years (interquartile range, 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). Patients with headache tended to have a slightly reduced risk of fatal or nonfatal myocardial infarction (adjusted HR, 0.88; 95% CI, 0.67–1.14). No difference between the 2 groups was found in the risk of fatal or nonfatal stroke (adjusted HR, 0.97; 95% CI, 0.76 to 1.24).

### Table 1. Baseline Characteristics of the 2473 Patients According to the Presence or Absence of Transient Ischemic Attack (TIA) or Minor Stroke–Related Headache

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Headache, n=420</th>
<th>No Headache, n=2053</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y; SD)</td>
<td>63.3 (10.5)</td>
<td>65.6 (10)</td>
</tr>
<tr>
<td>Men</td>
<td>258 (61%)</td>
<td>1350 (66%)</td>
</tr>
<tr>
<td>History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>54 (13%)</td>
<td>205 (10%)</td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>22 (5%)</td>
<td>106 (5%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>28 (7%)</td>
<td>174 (8%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>151 (36%)</td>
<td>889 (43%)</td>
</tr>
<tr>
<td>Angina</td>
<td>56 (13%)</td>
<td>198 (10%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>17 (4%)</td>
<td>77 (4%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>181 (43%)</td>
<td>944 (46%)</td>
</tr>
<tr>
<td>Event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor ischemic stroke</td>
<td>314 (75%)</td>
<td>1400 (68%)</td>
</tr>
<tr>
<td>TIA</td>
<td>106 (25%)</td>
<td>653 (32%)</td>
</tr>
<tr>
<td>Rankin grade ≥2</td>
<td>106 (25%)</td>
<td>466 (23%)</td>
</tr>
<tr>
<td>Visual disturbances only</td>
<td>23 (5%)</td>
<td>139 (7%)</td>
</tr>
<tr>
<td>Pure motor symptoms</td>
<td>159 (38%)</td>
<td>866 (42%)</td>
</tr>
<tr>
<td>Pure sensory symptoms</td>
<td>24 (6%)</td>
<td>103 (5%)</td>
</tr>
<tr>
<td>Sensory-motor symptoms</td>
<td>136 (32%)</td>
<td>668 (33%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>77 (18%)</td>
<td>184 (9%)</td>
</tr>
<tr>
<td>Paresis</td>
<td>276 (66%)</td>
<td>1487 (73%)</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>94 (22%)</td>
<td>494 (24%)</td>
</tr>
<tr>
<td>Aphasia</td>
<td>79 (19%)</td>
<td>400 (20%)</td>
</tr>
<tr>
<td>Lacunar syndrome</td>
<td>188 (45%)</td>
<td>1182 (58%)</td>
</tr>
<tr>
<td>Verteobasilar syndrome</td>
<td>70 (17%)</td>
<td>212 (10%)</td>
</tr>
<tr>
<td>12-lead ECG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q wave</td>
<td>56 (13%)</td>
<td>299 (15%)</td>
</tr>
<tr>
<td>ST-depression</td>
<td>36 (9%)</td>
<td>175 (9%)</td>
</tr>
<tr>
<td>Negative T wave</td>
<td>52 (12%)</td>
<td>197 (10%)</td>
</tr>
<tr>
<td>Acute phase hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure &gt;160 mm Hg</td>
<td>184 (44%)</td>
<td>1077 (52%)</td>
</tr>
<tr>
<td>Diastolic blood pressure &gt;90 mm Hg</td>
<td>254 (60%)</td>
<td>1297 (63%)</td>
</tr>
</tbody>
</table>
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 nonvascular death. The nonparametric 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 2 groups at any time period (at 5, 10, and 15 years, $P=0.60$; $P=0.25$; $P=0.35$, respectively).

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 vertebrobasilar 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 ischemic stroke was associated with headache had a reduced long-term risk of recurrent vascular events compared with those without headache. This effect seems mainly because of 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 in comparing the long-term vascular prognosis of ischemic 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. Previous studies that focused on short-term outcome found no relationship between concomitant headache and stroke severity as well as in-hospital mortality and 6 months outcome. 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.

This 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 noncardioembolic 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 Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria were published, and no formal classification of stroke source was recorded. In the trial, patients with cerebral ischemia because of identifiable causes other than arterial thrombosis or arterial embolism, including atrial fibrillation, were excluded; and therefore, the participants of our study have cerebral ischemia 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.

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 ischemic stroke and participants with or without ischemic lesions on the CT scan (Figure 2).

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, present more often with headache than others and are also associated with better long-term prognosis after the event. Although arterial dissection and reversible cerebral vasoconstriction syndrome are relatively rare causes of ischemic stroke, we cannot exclude that they have played a role in our results.

It has been proposed that headache related to stroke is because of stimulation of sensory afferents of the trigeminovascular system. The stimulation could be either directly by ischemia or indirectly by factors associated with ischemia. One factor that might play a role in the indirect stimulation of the trigeminovascular system is cortical SD. 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. 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 ischemia, predisposing them to strokes during mild ischemic events.28,29 Second, SD was found in the penumbra of nonmigrainous 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 hyper-tension.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 ischemic stroke with concomitant headache reflects a different subtype of stroke compared with stroke related to other mechanisms, such as atherosclerosis. Future studies are required to confirm this.

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Disclosures

None.

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