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**Are migraine and non-migrainous headache risk factors for stroke in the elderly?**

**Findings from a 12 year cohort follow-up.**

Joanna Norton, PhD\*<sup>1,2</sup>, Florence Portet, MD PhD<sup>1,2</sup>, Audrey Gabelle, MD PhD<sup>2,3,4</sup>,  
Stephanie Debette, MD PhD<sup>5,6</sup>, Karen Ritchie, PhD<sup>1,2,7</sup>, Jacques Touchon, MD<sup>1,2,3</sup>, Claudine  
Berr, MD PhD<sup>1,2,3</sup>

<sup>1</sup>Inserm U1061, Montpellier, France

<sup>2</sup>University of Montpellier, France

<sup>3</sup>Memory Resources Research center, Neurology Department, University Hospital Gui de  
Chauliac, Montpellier, France

<sup>4</sup>Inserm U1183, Montpellier, France

<sup>5</sup>Inserm U897, Bordeaux, France

<sup>6</sup>University of Bordeaux, France

<sup>7</sup>Faculty of Medicine, Imperial College, London, UK

\*Corresponding author

Inserm U1061, Neuropsychiatry: epidemiological and clinical research

Hôpital La Colombière Pav. 42

39 av. Charles Flahault

34093 Montpellier Cedex 5, France

Tel: +33499614570 Fax: +33499614579

joanna.norton@inserm.fr

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**Abstract**

**Background:** There is evidence that migraine is a risk factor for stroke but little is known about this association in elderly people. Furthermore, non-migrainous headache (NMH) has received little attention as a potential risk factor, despite being the most frequently reported type of headache. Late-life migraine and NMH were examined as candidate risk factors for stroke in a community-dwelling elderly sample over a 12-year follow-up.

**Methods:** 1919 non-institutionalized subjects 65+, without dementia (DSM-IV criteria) and no stroke history at baseline were drawn from the 3C-Montpellier cohort (recruitment 1999-2001) for the longitudinal analysis. Ischemic and haemorrhagic stroke was reported at baseline, and at each of the 5 follow-ups, with ICD-10 cases validated by a panel of experts. Migraine and NMH were determined at baseline during a neurological interview and examination using 1988 IHS criteria.

**Results:** 110 (5.4%) cases of migraine and 179 (8.9%) cases of NMH were identified at baseline. During the median 8.8 year follow-up, incident stroke was observed in 1.9% of baseline migraineurs, 6.2% of NMH and 3.6% of those with no lifetime history of headache. Cox proportional hazard models indicated that migraine was not a risk factor for stroke, however NMH sufferers were twice as likely to have a stroke (Hazard Ratio=2.00, 95% CI: 1.00-3.93,  $p=0.049$ ).

**Conclusions:** This study is one of the first to suggest that late-life NMH rather than migraine could be an independent risk factor for stroke and warning sign. The incidence of stroke in elderly migraineurs, seldom reported, is particularly low.

## Introduction

Migraine and non-migrainous headaches (NMH) are common disorders in the elderly. They are often chronic and can cause considerable disability [1]. NMH frequencies are seldom reported [2-4], but appear to be at least twice as high as those for migraine (26% versus 12% among 20 year olds and above) [2]. In women above age 45, NMH represent 73.8% of all headaches [5]. Both NMH and migraine decrease after age 60 [2]. However, migraine still affects 7% of women and 3% of men over 65 [6] and NMH 18.1% of women and 11.7% of men aged 70-79 [2].

Migraine is now a well-established risk factor for stroke [3,7-13], specifically when accompanied by aura and in women [7,12,14,15]. Whilst many studies have observed an association between migraine and ischemic stroke [3,12,14], evidence is less consistent for haemorrhagic stroke [11,16] and for migraine without aura [7,8,12,14]. There is even less evidence for NMH [17-20], despite being associated with a pathological cardiovascular risk profile [20]. Kurth et al. found no increased risk of ischemic stroke with NMH in a prospective study of men aged 40-84 [3], confirmed in a similar study of women aged 45+ where no association was found between NMH and total, ischemic and haemorrhagic stroke [5]. A more recent study found no difference in cardiovascular mortality between subjects with migraine, NMH and without headaches [21].

Although some studies have included elderly subjects [3,7,12,15,22], few have focused specifically on this age group in which stroke is a major public health concern. Hall et al. report an increased risk of incident stroke with migraine, which remains significant in the 60+ age group [22]. To the best of our knowledge, Mosek et al.'s case-control study is the only study performed specifically in the elderly and suggests that elderly headache sufferers, whatever the type of headache, are not at an increased risk of a stroke.

Given that the link between headache and stroke remains poorly explored in the elderly, we aim to describe the pattern of migraine and NMH in this age group and establish their long-term temporal relationships to stroke, taking into account multiple confounding factors.

## **Methods**

### **Study sample and data collection**

In the Montpellier centre of the 3C study [23], community-dwelling persons 65 years and over were randomly selected from the fifteen electoral rolls of the Montpellier District between March 1999 and February 2001. An invitation letter to participate was sent to all eligible subjects who were invited to attend a half-day clinical examination. The baseline sample included 2259 subjects with follow-ups at 2, 4, 7, 9 and 11 years.

At baseline, a face-to-face standardized interview [24] covered socio-demographics, lifestyle characteristics, present state of health, personal and family medical history and current and past month medication coded with the Anatomical Therapeutic Chemical (ATC) classification. Subjects were asked to report treatment or follow-up for health conditions including hypertension, diabetes, hypercholesterolemia, history of cerebro- and cardiovascular diseases. A standardized neuropsychiatric interview and examination was performed by a trained neurologist.

The cross-sectional analysis was performed on 2052 participants free of DSM-IV criteria dementia at inclusion (70 excluded) with at least one follow-up examination (136 excluded) and a baseline neurological examination (1 excluded). A sensitivity analysis showed that the 136 subjects lost to follow-up excluded from the analysis were significantly older ( $p < 0.0001$ ), living alone ( $p = 0.02$ ) with a lower level of education ( $p = 0.006$ ), lower income ( $p = 0.0002$ ), higher frequencies of cardiovascular disease ( $p < 0.0001$ ), hypertension

( $p=0.02$ ), disability ( $p<0.0001$ ), cognitive impairment ( $p<0.0001$ ) and anxiolytic medication consumption ( $p=0.03$ ). There were no significant differences for current or lifetime NMH and migraine.

The longitudinal analysis was performed on 1919 subjects with no history of stroke at baseline and no missing values for the main covariates. The median (min-max) follow-up time was 8.8 (0.6-11.7) years.

## **Variables**

### Migraine and NMH

During the baseline face-to-face standardized neurological examination, subjects were questioned about past and current headache episodes and a specific questionnaire was completed allowing cases to be classified as follows, based on the International Headache Society (IHS) guidelines available at the time [25]:

- Baseline or current headache (Migraine or NMH but not both) referring to at least one clinically significant episode in the past 6 months, and thus reflecting both continuation of lifetime (past) episodes and late-life onset.
- past episodes of migraine or NMH, for which the questionnaire was completed only in the absence of current headache.
- Lifetime headache including all subjects with either current or past episodes of migraine or NMH, respectively.

Among subjects reporting headaches, a diagnosis of NMH was made only after excluding a diagnosis of migraine. Subjects were asked the age at the onset of symptoms and for how many years they had experienced headaches. Factors that could trigger headache attacks were also identified during the standardized interview. For women, the

role of hormonal factors was evaluated. For migraine, data were collected on associated aura, symptoms and disabilities; and for NMH on aetiology.

#### Ascertainment of stroke cases

At baseline any lifetime episode of stroke was reported in the standardized health questionnaire. At each follow-up examination, subjects reported episodes that occurred since the previous visit (during interview or by self-report questionnaire), helped by further medical data collected from general practitioners, specialists and hospital records when possible, in order to confirm the diagnosis. Cases of stroke at follow-up also included fatal strokes (death within 28 days). Expert panels reviewed all available clinical information and classified each event according to ICD-10 (International Classification of Diseases, 10th revision) [26]. Brain imaging data were available for more than 80% of validated stroke cases (computerised tomography 82%; magnetic resonance imaging 15%) and Doppler ultrasound for 62%. When no brain imaging was available, the diagnosis was based on signs and symptoms. Stroke was confirmed if the participant had a new focal neurological deficit of sudden onset with no apparent cause other than that of vascular origin that persisted for more than 24 hours or leading to death [27]. The panel classified stroke as ischaemic stroke, intracerebral haemorrhage, or of unspecified type [28].

#### Other baseline variables

Cardiovascular disease at baseline included subjects reporting at least one of the following conditions: treatment or follow-up for heart failure, abnormal cardiac rhythm, peripheral artery disease, a history of myocardial infarction, coronary angioplasty or coronary artery bypass graft and angina pectoris. Chronic disease included any one of the following: diabetes (fasting glycaemia >7mmol/l or treated), respiratory disorders (asthma, chronic



bronchitis), thyroid disorder and cancer. We also considered hypertension (>160/95 mm Hg or treated) and hypercholesterolemia (cholesterol>6.2 mM, or treated).

Depressive symptomatology was assessed by the Center for Epidemiological Studies scale validated in French [29]. Spielberger's Trait Anxiety Inventory [30] was used to measure anxiety, comparing scores in the highest tertile to the lowest two. Depressive symptomatology and antidepressant use were grouped into a single variable (CESD score $\geq$ 16 or antidepressant use).

The study protocol was approved by the Ethical Committee of the University Hospital of Kremlin Bicêtre and Sud Méditerranée III (Nîmes). Each participant signed an informed consent form.

### **Statistical Analysis**

Frequency rates for baseline and lifetime migraine and NMH are given along with a detailed description of cases. Groups of subjects with migraine or NMH at baseline were each compared to unaffected subjects defined as those with no current or past episodes of migraine or NMH, using logistic regression models adjusted for age and sex, and further adjusted for history of stroke and other variables known to be associated with both headache and stroke.

The percentage of incident cases of stroke is given according to migraine and NMH at baseline and the Kaplan-Meier method was used to derive survival curves. Incident stroke is studied in subjects with baseline migraine and NMH respectively, each group being compared to unaffected subjects with no migraine or headache at baseline. The associations were tested with different levels of adjustment, entering variables that are well-known risk factors for stroke or identified as such with p-values <0.15. Cox-proportional hazard models were used with delayed entry taking age as the basic timescale and birth as the time origin. Model 1 is adjusted for sex, Model 2 is further adjusted for body mass index (BMI), current smoking,

cardiovascular pathologies, chronic disease and hypertension, and Model 3 for depressive symptomatology/antidepressant use and anxiety, both highly associated with NMH or migraine in the cross-sectional study. Interactions with sex, smoking and hypertension were tested and non-significant. Statistical analyses were performed using SAS version 9.4.

## **Results**

### **Frequency rates**

Lifetime migraine meeting IHS criteria was diagnosed in 357 participants (17.4%) and current migraine in 110 participants (5.4%). Regarding NMH, 233 (11.4%) lifetime and 179 (8.9%) current cases were diagnosed. The majority of subjects (95%) had only one type of headache diagnosed which was either current or past, only 28 (5%) had a combination of current NMH and past migraine.

Of subjects with current migraine, 68.8% had a family history of the disorder and 44.4% an age of onset below 20. For NMH, 31.1% had a family history of the condition and 68.2% an age of onset above 60. For both conditions, the most frequently reported precipitating factor was stress or anxiety (Table 1).

Of the migrainers, 9.8% had migraine with aura and 34.9% declared associated tension headaches. Only 4 (3.6 %) had not taken medication for their attacks in the past six months. Analgesic treatment was reported by 93.6%. The most frequently taken medications at baseline (1999-2000) were salicylic acid and derivatives (86.4%), anilides (73%), ergot alkaloids (41.4%), pyrazolones (22.5%) and opioids (8.1%).

Regarding baseline NMH, 36.5% were classified as tension headaches of which 7.3% with associated depression. Other types in order of importance were: rheumatology related NMH (25.1%), Arnold's neuralgia (12.9%), hypertension-related NMH (4.5%), glaucoma

related NMH (3.4%), trigeminal neuralgia (3.4%), intra-cranial NMH (3.4%), ear nose and throat related NMH (2.8%) and other aetiologies (5.6%).

### **Socio-demographic and clinical factors associated with current migraine and NMH**

Migraine and NMH specifically affect women; 47% of unaffected subjects were men, compared to 17.3% of migrainers and 30.7% of NMH (Table 2). Migrainers and NMH were also younger than unaffected participants with, for the NMH group, higher rates of chronic disease and hypertension. Compared to the unaffected group, both the NMH and migraine groups had higher rates of depressive symptomatology and trait anxiety. Antidepressant use was significantly higher for the NMH group only.

In the cross-sectional analysis, a history of stroke was reported by 3.2% of unaffected subjects, compared to 0.9% (1 subject) of migrainers and 7.9% of NHM subjects. This latter association with NMH remained significant when further adjusting for chronic disease, hypertension, cardiovascular disease, depressive symptomatology or antidepressant use, and anxiety ( $p=0.002$ ).

### **Migraine and NMH as risk factors for incident stroke**

There were 73 cumulated incident strokes over the follow-up period – 82.2% ischemic, 12.3% haemorrhagic and 5.5% undetermined - with a delay until the event of 5.8 (0.6-11.7) years. Of baseline migrainers, 1.9% (2/106) had a stroke during follow-up, compared to 6.2% (10/161) of baseline NMH sufferers, 4.3% (11/258) of subjects with past migraine or NMH. The crude comparison of the Kaplan-Meier survival curves according to baseline NMH (Figure 1) suggests a greater probability of stroke in the early years of follow-up among NMH subjects.

Baseline NMH was significantly associated with a higher risk of stroke whatever the level of adjustment (Table 3). In Model 3, the 12-year risk of stroke among NMH sufferers was twice as high as among unaffected subjects (HR=2.00, 95% CI: 1.00-3.93, p=0.049). A sensitivity analysis excluding the 258 subjects with past migraine or NMH showed unchanged results (not shown).

## **Discussion**

Epidemiological studies have seldom examined the association of both NMH and migraine with stroke specifically in the elderly, considering late-life (65+) migraine and NMH as independent risk factors for stroke. Few findings have been published on NMH and cerebro-cardiovascular disease, yet the limited data available suggests this type of headache to be at least twice as frequent as migraine [2,5]. One of our main findings is a low incidence of stroke in elderly migraineurs. In contrast, to the best of our knowledge, this is the first study showing NMH to be a risk factor for late-life stroke after controlling for age, sex, BMI, smoking status, cardiovascular pathologies, chronic disease, depression and anxiety.

In our sample, the incidence of stroke among migraineurs is low, lower than both the rate among NMH subjects and that among unaffected migraine and NMH subjects. It is in keeping with the low risk of haemorrhagic stroke found among middle-aged women (mean 54.9) with migraine [15]. As in a recent study [31], we found no overall association between migraine and stroke. However, the evidence for a link between the two is often limited to migraine with aura and female gender [5,15] and younger age groups [7,14,15], and the risk is greatly increased when migraine is combined with smoking, oral contraceptive use and high blood pressure [14]. Due to small numbers, we were not able to stratify the sample according to type of migraine (with/without aura) or sex.

In a cross-sectional study examining the Framingham risk score for myocardial infarction and coronary death in middle-aged subjects, a higher risk score for NMH was found, which became non-significant when adjusting for unhealthy lifestyle factors [20]. Scher et al. in a cohort of 33- 65 year olds found no association between NMH and risk of late-life MRI identified infarct-like lesions [19]. Two cohort studies in women aged 45+ [5] and men aged 40-84 [3] evaluated the risk of stroke with NHM. Despite controlling for numerous potential confounders, neither found an association whatever the type of stroke. In both these cohorts of health professionals headaches were self-reported with possible cases of underreporting and misclassification. In our study, we adjusted for a number of baseline lifestyle and clinical factors linked both to NMH and stroke incidence. However, it is possible that these risk factors may have evolved over time, along with the frequency of NMH, impacting the onset of stroke. Also, despite the long follow-up, participants with specific types of NMH such as hypertension-related NMH may already have been at higher risk of stroke at baseline and may have experienced minor strokes. We thus carried out a sensitivity analysis excluding participants with arterial hypertension NMH (N=8). The results were not altered suggesting the extent of this bias is minimal. Moreover, changing the threshold for hypertension (140/90) did not modify the results. Hypotheses as to a causal pathway between NMH and stroke remain largely unexplored, due to the lack of studies on this topic and to the heterogeneity of NMH [32] which is not a clearly defined diagnostic entity.

Our study is one of the few carried out specifically in the elderly. Mosek et al. found no association between migraine and stroke, but relied on recall for headache history in a case-control design in a highly selected elderly clinical population [18]. However, no adjustment factors other than age and sex were taken into account and headache history was reported subjectively. Hall et al. in a matched case-control study (with a mean follow-up of

approximately 3 years) found migraine to be a risk factor for stroke in the 60+ age group in both men (adjusted HR: 1.89, 95% CI: 1.23-2.91) and women (HR: 1.30 (1.01-1.67)) [22]. It can be argued however that the short follow-up may make it difficult to discern between migraine and minor stroke with headache prior to the event.

The main limitation of our study is the small number of events at follow-up (n=73), specifically among subjects with migraine (n=2). These small numbers did not allow us to rule out an association between migraine and stroke, or stratify the analysis according to the subgroups most at risk (migraine with aura, female gender). Furthermore, we were not able to study headache starting in late-life only because of lack of precision on age of onset. We may have underestimated the association between headache and stroke due to classification bias, as participants receiving medication for past headaches may have been classified at baseline in the non-headache group, yet some pain relief medications may increase the risk of stroke [33]. It is difficult to quantify the extent of this bias given that many medications for NMH are non-specific with various indications; furthermore non-headache participants were not asked the reason or indication for which they were taking each medication.

Another major limitation is the heterogeneity of the NMH category, which makes it difficult to interpret our findings. Of the NMH, 36.5% were classified as tension headaches, the remaining presenting a wide range of pathogeneses. Unfortunately we did not have the statistical power to perform subgroup analyses. A further limitation is the timing of the clinical assessment of headaches, based on the 1988 International Classification of Headache Disorders criteria [25] which were the standard guidelines at the time. These have been updated twice since [32,34]. Modifications are considered to be relatively small, concerning mainly new and specific sub-types of headaches rather than overall diagnostic criteria.

On the other hand, we were able to integrate the use of a clinical diagnostic tool, in a one-step neurological examination using IHS criteria, in a large-scale epidemiological study. Other studies have used self-report [31] or mail questionnaires [35], which may be less valid and accurate. Evidence for the association between migraine and stroke is often based on case-control studies [7,8,18,35] with possible recall bias regarding past migraine, which we can rule out in our prospective study. Furthermore, contrary to studies relying only on self-report [17], cases reporting stroke were validated by a panel of experts [28].

In sum, our findings are novel in reporting a low incidence of stroke in elderly migraineurs. The incidence among NMH subjects is three-fold higher. This highlights the need to follow more closely elderly people with this type of headache which is often considered common and of lesser importance. Although the overall risk of stroke is relatively weak, it could be doubled in the case of NMH which should therefore be considered of clinical relevance as a warning sign and investigated alongside other stroke risk factors. Further prospective studies are needed with larger samples in order to investigate the risk per stroke aetiology associated with the specific types of NMH.

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Table 1. Main clinical characteristics of subjects with current migraine and NMH at baseline

	Migraine %	N	NMH %	N
Age (mean (sd))	71.74 (4.75)	110	72.21 (5.22)	179
Sex (male)	17.27	110	30.73	179
Family history (yes)	68.81	109	31.07	177
Age at onset				
<20	44.44		2.31	
20-39	39.81		7.51	
40-59	12.96		21.97	
≥60	2.78	108	68.21	173
Duration > 10 years (yes)	98.15	108	43.93	173
Chronicity (yes)	30.10	103	59.06	171
<b>Handicap in life</b>				
Limitation in leisure/work	48.62	109	6.15	179
Bedridden	40.91	110	3.93	178
Hospitalisation	0.91	110	0.56	179
<b>Lifetime precipitating factors</b>		108		177
None	12.96		42.94	
Stress or anxiety	68.52		31.07	
Changes in life habits	37.96		9.60	
Specific nutrients	26.85		1.69	
Nutritional change	20.37		1.13	
Hormonal factors (women)	24.07		0.0	
Sensorial factors	13.89		1.69	
Climatic factors	17.59		26.55	
Drugs + iatrogenic	0.93		0.56	

Table 2. Characteristics of subjects according to baseline migraine and NMH following IHS criteria compared to unaffected subjects (N=1784 after exclusion of subjects with only past NMH or past migraine)

Variable	Unaffected subjects (1) (N=1495) <sup>±</sup>		Migraine (2) (N=110) <sup>±</sup>		NMH (3) (N=179) <sup>±</sup>		p* (1 v. 2)	p* (1 v. 3)
	n	%	n	%	n	%		
Sex (male)	703	47.02	19	17.27	55	30.73	<.0001	<.0001
Age (mean (sd))	73.14 (5.53)		71.74 (4.75)		72.21 (5.22)		0.01	0.03
Education								
Low	366	24.50	32	29.10	52	29.05		
Medium-low	418	27.98	28	25.45	57	31.84		
Medium-high	331	22.16	28	25.45	39	21.79		
High	379	25.36	22	20.0	31	17.32	0.54	0.32
BMI ( $\geq 25$ )	698	47.10	45	41.28	85	47.49	0.81	0.45
Alcohol (>12g/day)	599	40.83	31	29.25	58	32.77	0.80	0.74
Current smoker (yes)	110	7.36	6	5.45	10	5.59	0.75	0.55
At least 1 chronic disease (yes)	328	21.94	20	18.18	54	30.17	0.42	0.01
Hypertension (yes)	653	43.68	42	38.18	89	49.72	0.71	0.02
Hypercholesterolemia (yes)	807	54.42	66	60.55	106	59.22	0.92	0.76
Cardiovascular disease (yes)	301	20.13	24	21.82	35	19.55	0.35	0.76
Stroke (yes)	47	3.18	1	0.92	14	7.87	0.43	0.0001
Current use of HRT (women)(yes)	116	14.89	16	18.18	19	16.38	0.94	0.84
Depressive symptomatology	409	27.58	46	42.59	75	43.37	0.008	0.0003
Spielberger Trait anxiety (yes)	409	28.05	53	48.18	79	45.14	0.002	0.0001
Antidepressant use (yes)	81	5.42	12	10.91	20	11.17	0.10	0.009
Anxiolytic use (yes)	154	10.30	17	15.45	25	13.97	0.20	0.21

<sup>±</sup> None of the variables have more than 5% missing values

\* p-values adjusted for age and sex

Table 3. Multi-adjusted associations of baseline migraine and NMH with incident stroke over the 12 year follow-up (N=1919)\*

Baseline variables	Incident Stroke				Model 1	Model 2 <sup>#</sup>	Model 3 <sup>#</sup>
	No		Yes		HR (95% CI), p (1)		
	n	%	n	%	HR (95% CI), p (1)	HR (95% CI), p (2)	HR (95% CI), p (3)
Unaffected subjects <sup>±</sup>	1591	96.31	61	3.69	1	1	1
Migraine	104	98.11	2	1.89	1.43 (0.35–5.87) 0.62	-	-
NMH	151	93.79	10	6.21	2.10 (1.07–4.11) 0.03	2.04 (1.04–4.02) 0.039	2.00 (1.00 – 3.93) 0.049

<sup>±</sup> with no baseline migraine or NMH

\* After exclusion of subjects with baseline history of stroke, we performed the analysis on subjects with data on stroke status at at least one follow-up and no baseline missing data for the adjustment variables.

<sup>#</sup> not performed for Migraine due to low numbers

p(1) : Model 1: adjusted for sex

p(2) : Model 2: adjusted for sex, BMI (<25 versus ≥25), smoking status, cardiovascular pathologies, chronic disease, hypertension

p(3) : Model 3: adjusted for sex, BMI (<25 versus ≥25), smoking status, cardiovascular pathologies, chronic disease, hypertension, depressive symptomatology or antidepressant use, trait anxiety

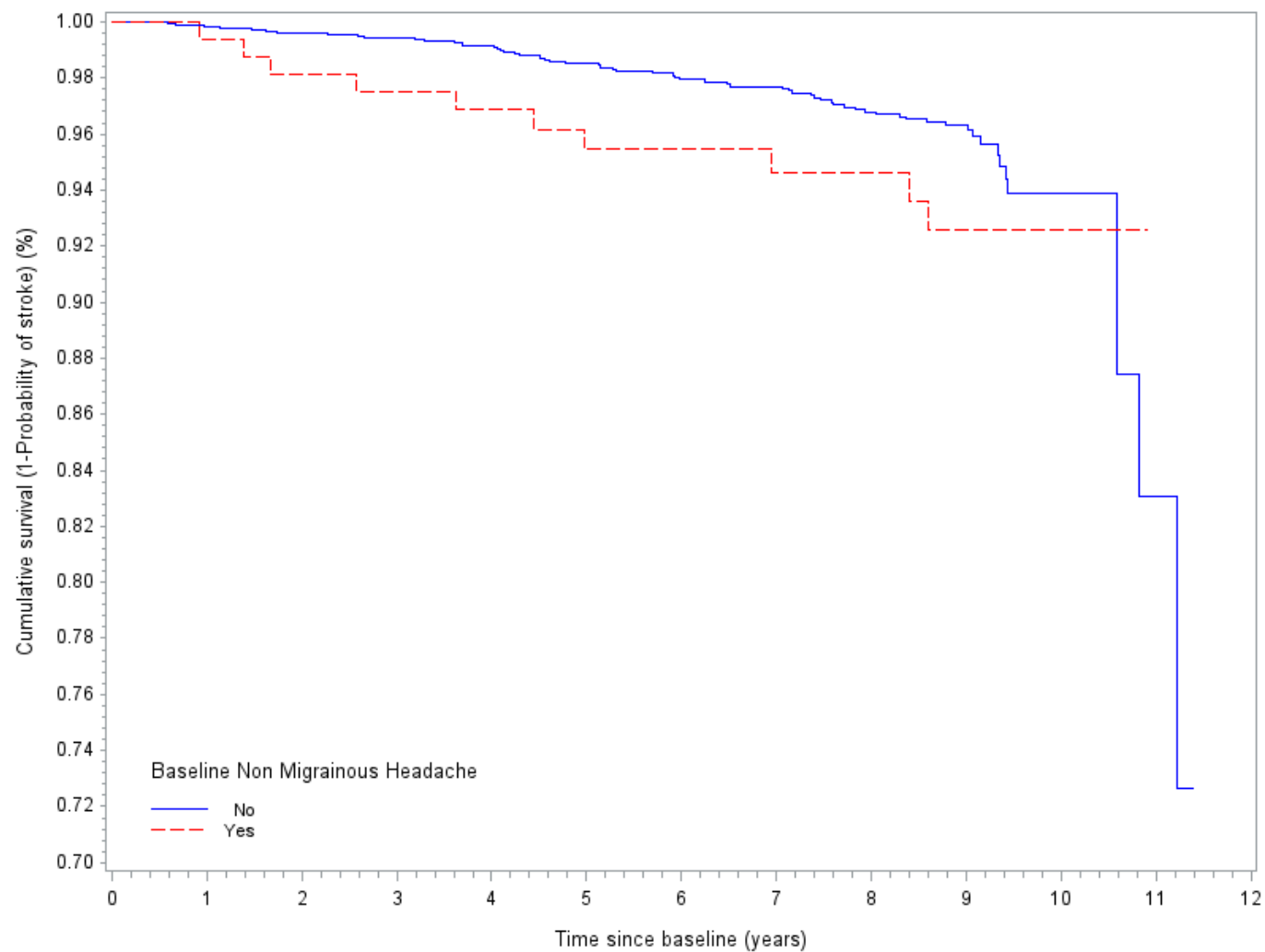


Figure 1. Kaplan-Meier survival curves for incident stroke by baseline NMH  
 Note: there were no more incident stroke cases among the NMH sufferers after 8 years of follow-up