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Migraine and Cardiovascular Disease in Women: the Role of Aspirin – Subgroup Analyses in the Women’s Health Study

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Abstract

Background—Migraine with aura (MA) has been associated with increased risk of cardiovascular disease (CVD). The role of aspirin on this association remains unclear.

Methods—Post-hoc subgroup analyses of the Women’s Health Study, a randomized trial testing 100mg aspirin on alternate days in primary prevention of CVD among 39,876 women aged ≥ 45 .

Results—During 10 years, 998 major CVD events were confirmed in 39,757 women with complete migraine information. Aspirin reduced risk of ischemic stroke (RR=0.76; 95% CI=0.63–0.93) but not other CVD. Migraine or MA did not modify the effect of aspirin on CVD except for myocardial infarction (MI) (p-interaction=0.01). Women with MA on aspirin had increased risk of MI (RR=3.72, 95% CI=1.39–9.95). Further exploratory analyses indicate this is only apparent among women with MA on aspirin who ever smoked or had history of hypertension (p-interaction<0.01).

Conclusion—In post-hoc subgroup analyses, aspirin had similar protective effects on ischemic stroke for women with or without migraine. By contrast, our data suggest that women with MA on aspirin had increased risk of MI. The small number of outcome events in subgroups, the exploratory nature of our analyses, and lack of plausible mechanisms raise the possibility of a chance finding, which must caution the interpretation.

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Migraine has been associated with increased risk of stroke, silent brain lesions, and other cardiovascular disease events [1–6]. In most studies, this association is only apparent among those who have migraine with aura and the absolute risk increase is considerably low. Despite a large body of literature, the reason for the increased risk of vascular events for migraineurs with aura remains unclear. Some data suggest involvement of cardiovascular risk factors [7, 8], genetic factors [9, 10], the endovascular system [11–13], prothrombotic markers [14–16], paradox embolization [17], or others [18]. It remains further unclear whether preventing migraine has any influence on vascular event occurrence.

Since many decades, low-dose aspirin is used to prevent ischemic cardiovascular disease events [19] because of its ability to irreversibly block the active site of the isoenzyme cyclooxygenase-1, resulting in reduced likelihood of platelet aggregation [20]. As there is some evidence that low-dose aspirin results in normalization of increased tendency of platelet aggregation [14] and also may reduced migraine attack frequency [21–23], the clinical question arises whether patients with migraine, specifically migraine with aura should use low-dose aspirin to have a beneficial effects on migraine frequency and to prevent subsequent cardiovascular disease. However, as the vascular event rate among migraineurs is low and low-dose aspirin also increases bleeding risk [19] uncertainties remain whether patients with migraine with aura should receive low-dose aspirin to prevent vascular events.

The Women’s Health Study provides an opportunity to explore whether randomization to low-dose aspirin assignment has beneficial effects in the primary prevention of CVD according to migraine status among initially health women.

Methods

Post-hoc subgroup analysis in the Women’s Health Study, which was a two-by-two factorial trial evaluating the effects of low-dose aspirin (100 mg every other day; Bayer HealthCare) and vitamin E (600 IU every other day; National Source Vitamin E Association), in the primary prevention of cardiovascular disease and cancer. The design and main results of the trial have been published previously [24–27]. In brief, between September 1992 and May 1995, letters of invitation were mailed to more than 1.7 million female health professionals. A total of 453,787 completed the questionnaires, with 65,169 initially willing and eligible to enroll. Women were eligible if they were 45 years of age or older; had no history of coronary heart disease, cerebrovascular disease, cancer (except nonmelanoma skin cancer), or other major chronic illness; had no history of side effects to any of the study medications; were not taking aspirin or nonsteroidal antiinflammatory drugs more than once a week (or were willing to forego their use during the trial); were not taking anticoagulants or corticosteroids; and were not taking individual supplements of vitamin A, E, or beta carotene more than once a week.

A total of 39,876 women were willing, eligible, and compliant during a placebo run-in period and were randomized: 19,934 were assigned to receive aspirin and 19,942 to receive placebo. Written informed consent was obtained from all participants. The trial was approved by the institutional review board of Brigham and Women’s Hospital, Boston, MA, and was monitored by an external data and safety monitoring board.

Every 12 months, the women were sent questionnaires on compliance, side effects, the occurrence of relevant clinical end points, and risk factors. Study medications and end-point ascertainment were continued in a blinded fashion through the scheduled end of the trial (March 31, 2004). Morbidity follow-up rates were complete for 97.2% and mortality follow-up rates for 99.4%.

Migraine ascertainment

On the baseline questionnaire, participants were asked: “Have you ever had migraine headaches?” and “In the past year, have you had migraine headaches?” We distinguished between women without migraine history, and those who reported any migraine history, active migraine (migraine in the year prior to completing the baseline questionnaire), or prior migraine (those who reported ever having had a migraine but none in the year prior to completing the questionnaire). Those participants who reported active migraine were further asked details about their migraine attacks, including attack duration of 4 to 72 hours; unilateral location and pulsating quality of pain; interference with daily activities; aggravation by routine physical activity; nausea or vomiting; and sensitivity to light or sound. Furthermore, participants who reported active migraine were asked whether they had an “aura or any indication a migraine is coming.” Responses were used to classify women who reported active migraine into active migraine with aura and active migraine without aura, as in other studies [1, 8, 28].

In a previous study [1], we have shown that among WHS participants who reported active migraine, 83.5% fulfilled all but one International Classification of Headache Disorders-I criteria [29] (code 1.7, migrainous disorder) and 46.6% fulfilled all criteria for migraine (code 1.1 migraine without aura). In addition, we showed [30] that in a subsample of the WHS 87.7% of women with self-reported active migraine could be diagnosed as migraine without aura (71.5%) or probable migraine without aura (16.2%) according to International Classification of Headache Disorders-II criteria [31].

Cardiovascular disease outcomes

All the women were followed for first occurrence of myocardial infarction, stroke, or death from cardiovascular causes. Medical records were obtained for all women in whom a cardiovascular end point was reported to occur and were reviewed by an end-points committee of physicians who were blinded to randomized treatment assignments. Myocardial infarction was confirmed if symptoms met World Health Organization criteria and if the event was associated with abnormal levels of cardiac enzymes or diagnostic electrocardiograms. A confirmed non-fatal stroke was defined as a new focal-neurologic deficit of sudden or rapid onset that persisted for at least 24 hours. Clinical information and brain imaging were used to distinguish hemorrhagic from ischemic events with excellent interrater agreement [32]. Symptoms of ischemic stroke lasting for less than 24 hours were confirmed as transient ischemic attacks. Death was confirmed to be from cardiovascular causes on the basis of an examination of autopsy reports, death certificates, medical records, and information obtained from the next of kin or other family members. The use of coronary revascularization (bypass surgery or percutaneous coronary angioplasty) was confirmed by a review of the medical records. Only confirmed end points were included in this analysis.

Statistical analysis

We excluded 119 women (65 on aspirin, 54 on placebo), for whom migraine information was missing, leaving 39,757 women for analysis. We calculated proportions and mean values for baseline characteristics according to aspirin and placebo assignment, stratified by migraine and migraine aura status. We used Cox proportional hazards models to evaluate the relative effect and 95% confidence interval for the comparison of outcome event rates in the aspirin and placebo group, adjusting for age and other randomized treatment assignments (vitamin E and beta-carotene which was a component of the trial for a median of 2.1 years [33]). The proportional hazards assumption was not significantly violated. To test whether the effect of aspirin on cardiovascular disease events differs according to migraine and migraine aura status, we contrasted a main effect model to a model that included aspirin-migraine status interaction terms by using the likelihood ratio test. We ran stratified models

testing the effect of aspirin on cardiovascular disease events in the subgroups ‘no history of migraine,’ ‘migraine with aura,’ ‘migraine without aura,’ and ‘prior migraine.’ Because of imbalances of the distribution of some baseline variables in the migraine with aura group (Table 1), we additionally adjusted the stratified models for any indication of history of hypertension, systolic blood pressure, and body mass index ≥ 30 kg/m².

In further exploratory analyses, we evaluated potential effect modification of the effect of aspirin on cardiovascular disease events among migraine with aura (ie, the only migraine subgroup associated with cardiovascular disease events in the Women’s Health Study) by age (<65 years vs. 65 years or older), history of hypertension (yes, no), ever smoked cigarettes (yes, no), and body mass index of 30 kg/m² or more, using the likelihood ratio test.

We performed a sensitivity analysis to evaluate the effect of compliance to randomized aspirin assignment by censoring follow-up data for women who reported having taken less than two thirds of the study medication during the previous year. All analysis followed the intention-to-treat principal and we considered a two-tailed P value < 0.05 as significant. We used SAS version 9.2 for all analyses.

Results

Of the 39,757 women with complete information on migraine status, 7,330 (18.4%) reported any history of migraine. A total of 5,174 women reported migraine in the year prior to randomization, of whom 2059 (39.8%) reported aura systems; 2156 women reported prior migraine (history of migraine but no migraine in the year prior to randomization). Table 1 summarizes the distribution of baseline characteristics according to randomized aspirin assignment in strata of women without migraine, migraine with aura, migraine without aura, and prior migraine. In general, the distribution of all baseline variables is well-balanced in this large trial. In the subgroup of women with migraine with aura, systolic blood pressure, history of hypertension, and body mass index ≥ 30 kg/m² were unequally distributed.

The effect of randomized aspirin assignment on cardiovascular disease events in the entire analysis cohort is summarized in Table 2. Aspirin significantly reduced the risk of stroke, (relative risk 0.83, 95% confidence interval 0.69 to 0.99), particularly ischemic stroke (relative risk 0.76, 0.63 to 0.93). Further, the occurrence of transient ischemic attacks was significantly reduced (relative risk 0.78, 0.64 to 0.95). We found no significant effect modification by migraine and migraine aura status on the effect of aspirin on major cardiovascular disease (p for interaction 0.26), total stroke (p for interaction 0.48), ischemic stroke (p for interaction 0.82), hemorrhagic stroke (p for interaction 0.23), cardiovascular disease death (p for interaction 0.20), and coronary revascularization procedures (p for interaction 0.26), indicating similar protective effects of aspirin on ischemic stroke and transient ischemic attacks. The effect of aspirin was, however, significantly modified by migraine and migraine aura status for myocardial infarction (p for interaction 0.01) and transient ischemic attack (p for interaction 0.02).

Table 3 summarizes the effect of randomized aspirin assignment on cardiovascular disease events in strata of migraine and migraine aura status. For myocardial infarction, there was an increased risk for women with migraine with aura who were randomly assigned to aspirin (relative risk 3.72, 1.39 to 9.95) when compared with women with migraine with aura assigned to aspirin placebo. This increased risk was not seen in any other migraine status subgroup. In absolute terms, this risk translates to 15 additional events per 10,000 women with migraine with aura treated with aspirin per year (Table 4), or in other words for each 665 women with migraine with aura treated with aspirin, one additional myocardial

infarction occurred in the Women's Health Study. The modifying effect of the effect of aspirin on transient ischemic attack by migraine status was driven by the subgroup of women with migraine without aura. Here, those assigned to aspirin appeared to have particularly protective effects (relative risk 0.19, 0.07–0.57).

In further exploratory analyses, we evaluated whether the effect of aspirin on myocardial infarction was modified by age, history of hypertension, smoking, and obesity in the subgroup of women with migraine with aura. We found strong effect modification of the association between aspirin and myocardial infarction among women with migraine with aura by history of hypertension (p for interaction 0.01). Among women with migraine with aura who had a history of hypertension, all myocardial infarctions (n=12) occurred among those assigned to aspirin. There was further marginally significant effect modification by ever smoking status (p for interaction 0.09), indicating increases risk only among those women who ever smoked cigarettes. When combining history of hypertension and ever smoking cigarettes, the risk of myocardial infarction was substantially elevated for women with migraine with aura who were assigned to aspirin and who had these cardiovascular risk factors (relative risk 18.7, 2.5 to 140.2, p interaction <0.001). We found no significant effect modification by age (aged 65 or older vs. age less than 65) or body mass index ≥ 30 kg/m².

There was no indication that compliance changed the effect of randomized aspirin assignment on cardiovascular disease events in the entire study or in migraine subgroups. Specifically the result of increased risk of myocardial infarction by aspirin for women with migraine with aura remained unchanged (relative risk 3.75, 1.05 to 13.42).

Discussion

Results of the Women's Health Study show that randomization of 100 mg aspirin every other day reduces a women's risk of first stroke, particularly ischemic stroke, as well as transient ischemic attack but not other cardiovascular disease events [25]. Results of our post-hoc subgroup analyses show that women with migraine have similar protective effects on ischemic stroke and transient ischemic attack, independent of aura status. Our data further suggests that women with migraine with aura who have been randomly assigned to low-dose aspirin have increased risk of myocardial infarction. Further exploratory subgroup analyses of this unexpected result suggests that history of hypertension and smoking status may be involved.

Comparisons to previous studies

Several studies and a meta-analysis have shown that higher doses of aspirin can abort acute migraine attacks [34]. Previous studies evaluating the effect of regular intake of lower aspirin doses among patients with migraine have focused on reduction of migraine frequency but not on potential effects on vascular events. Some data [21, 35], including results from the Women's Health Study [22], suggest potential beneficial effects of lower aspirin doses on migraine frequency.

Strength and limitation

Strength of the study include the large sample of initially health women, the randomized, double-blind, placebo controlled design, verified outcome events, standardized migraine ascertainment, long follow-up, and high participation rates.

Several limitations have to be considered when interpreting our results. First, the Women's Health Study was not designed to test effects of aspirin on cardiovascular disease events among women with migraine or migraine aura status. In addition, the number of outcome events was limited in subgroups. Thus and despite statistical significance, our results must

be interpreted with caution. Second, migraine status was self-reported by participants and not classified according to strict International Headache Society criteria [31]. Although previous reports from this cohort have shown good agreement of migraine classification with modified International Headache Society criteria [1, 30], misclassification is possible. However, since our study design is prospective and treatment was assigned at random, such misclassification is expected to be non-differential and unlikely to explain the observed associations. Third, we had no further details on migraine aura in this cohort, which would have allowed us to classify participants according to International Headache Society criteria for aura, or to take aura frequency or other specifics into account. However, our prevalence of migraine with aura is in range with other population-based estimates [36, 37]. Finally, participants in the Women's Health Study were middle-aged, mostly white health professionals and thus generalizability to other female populations may be limited.

Interpretation of the results

For most cardiovascular disease events we find no evidence that the effect of aspirin on cardiovascular disease events differs among patients with migraine when compared to those without. In particular, our data provide evidence that the protective effect of aspirin on ischemic stroke and transient ischemic attack is also apparent among women with migraine, independent of migraine aura status. Subgroup analyses further suggest that the effect of aspirin on transient ischemic attacks may be stronger among women with migraine without aura. In contrast to primary prevention studies in men and in secondary prevention trials, results of the Women's Health Study overall do not show a benefit of low-dose aspirin on myocardial infarction. Potential reasons for this finding are manifold, including too low aspirin dosage, hormonal influences, or generally lower rate of myocardial infarction in women than in men. As aspirin significantly reduced all vascular events including myocardial infarction among women aged 65 and older in the Women's Health Study, effect modification by age may be another explanation. The suggested increased risk of myocardial infarction for women with migraine with aura who were randomly assigned to 100 mg aspirin every other day may be another reason why women overall may not have beneficial effects of aspirin on myocardial infarction. However, the reason for this increased risk is unclear.

To the best of our knowledge there is no known biological mechanism leading to an interference of the pharmacological effects of aspirin by migraine aura that would result in increased risk of ischemic events. It has been shown that patients with migraine have increased likelihood of platelet aggregation [14, 38], which may lead to conclusions that patients with migraine need somewhat higher doses of aspirin to reach protective effects against ischemic vascular events. However, one would expect at most a lack of effect of aspirin on vascular events but not to observe an increased risk. Even in combination with other factors, we would maximally expect to observe no effect of aspirin on vascular events. Potential factors inhibiting the effect of aspirin on cardiovascular disease event include concomitant non-steroidal anti-inflammatory drug use [39, 40], particularly ibuprofen, smoking [41], non-adherence [42], and so called resistance to aspirin [43].

Overall, we believe that in the light of lack of biological plausibility and the post-hoc subgroup analyses approach of our study, which increases a the likelihood of a chance finding, the most plausible explanation of the increased risk of myocardial infarction is a random data imbalance. However, we cannot exclude the possibility of unknown mechanisms increasing the risk of myocardial infarctions among patients with migraine with aura taking aspirin, which should lead to further targeted research.

Clinical Implication

Overall, our data indicate that the effect of aspirin on the primary prevention of cardiovascular disease does not depend on migraine or migraine aura status. In particular, the beneficial effect of aspirin on ischemic stroke and transient ischemic attack is not modified by migraine status. However, before considering giving low-dose aspirin to patients with migraine independent of the presence of other vascular risk factors, one has to consider that the absolute event rate of stroke and other vascular events for women with migraine with aura is considerably low [1] and low-dose aspirin utilization can increase bleeding risk [19]. Further, migraine with aura may by itself increase the risk of hemorrhagic stroke [44, 45]. Moreover, the association between migraine with aura and ischemic stroke is only apparent for strokes with good to excellent functional outcome, independent of aspirin intake [46]. Because of the unclear underlying biology, we believe that the increased risk of myocardial infarction for women with migraine with aura receiving aspirin should not be incorporated into current clinical decision making unless further evidence is available. We also have no reason to believe that our data extend to casual use of higher doses of aspirin to avert acute migraine attacks.

Further research directions

The association of migraine and migraine aura on endovascular function, stroke and other cardiovascular disease remains of substantial interest and further research should be targeted to explore potential biological mechanisms and to identify preventive strategies. Whether aspirin has different effects among patients with migraine should be further addressed to clarify remaining uncertainties.

In conclusion, in post-hoc subgroup analyses of this large trial, aspirin had similar protective effects on ischemic stroke for women with or without migraine. By contrast, our data suggest that among migraineurs with aura, aspirin increased the risk of myocardial infarction, possibly via interactions by smoking and hypertension. The small number of outcome events in subgroups, the exploratory nature of our analyses, and lack of plausible mechanisms raises the possibility of a chance finding, which must caution the interpretation. However, a potential harmful effect of aspirin on myocardial infarction in the small subgroup of women with migraine with aura warrant further targeted research.

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Table 1
Baseline characteristics according to randomized aspirin assignment and migraine status in the Women's Health Study (n=39,757).

Characteristics	No History of Migraine		Migraine With Aura		Migraine Without Aura		Prior Migraine*	
	Aspirin	Placebo	Aspirin	Placebo	Aspirin	Placebo	Aspirin	Placebo
No. of participants	16,241	16,186	1029	1030	1559	1556	1040	1116
Mean age, years (SD)	54.8 (7.2)	54.8 (7.2)	52.8 (6.1)	53.0 (6.0)	52.8 (6.0)	52.5 (5.5)	55.6 (7.2)	55.4 (7.5)
Mean systolic blood pressure, mm Hg (SD)	124.1 (13.9)	124.0 (13.8)	124.2 (13.5)	122.6 (13.0)	123.9 (13.7)	123.1 (13.7)	125.5 (14.3)	125.6 (14.1)
History of hypertension [†] , %	25.5	25.5	27.7	22.6	25.0	24.5	34.4	32.6
Body mass index, %								
<25 kg/m ²	51.3	50.8	47.3	51.8	48.0	50.7	50.5	51.2
25 – 29.9 kg/m ²	30.8	31.1	32.8	32.9	32.5	30.1	29.0	29.1
≥30 kg/m ²	17.9	18.1	19.9	15.3	19.5	19.2	20.5	19.7
Smoking, %								
Never	50.5	50.6	54.1	53.5	55.6	55.1	50.1	50.0
Past	36.3	36.1	33.7	33.7	33.9	34.0	36.1	33.6
Current	13.2	13.4	12.2	12.8	10.5	10.9	13.9	16.3
Premenopausal, %	27.5	27.4	28.9	29.3	30.5	32.2	21.4	22.9
Family history of myocardial infarction prior to age 60, %	11.6	11.3	13.6	13.0	11.7	12.5	11.1	13.1

SD denotes standard deviation

Proportions may not add-up to 100% due to rounding or missing values.

* Women who indicated a history of migraine but no active migraine in the previous year for whom we had no aura information.

[†] Hypertension was defined as systolic blood pressure of at least 140 mm Hg, a diastolic blood pressure of at least 90 mm Hg, or self-reported physician-diagnosed hypertension.

Table 2

Randomized aspirin assignment and risk of vascular events among participants with complete information on migraine status in the Women's Health Study (N=39,757)

	Aspirin N=19,869	Placebo N=19,888	Relative Risk* (95% CI)	P Value
Major cardiovascular event [†]	477	521	0.91 (0.80–1.03)	0.14
Stroke	221	266	0.83 (0.69–0.99)	0.04
Ischemic	170	221	0.76 (0.63–0.93)	0.009
Hemorrhagic	51	41	1.24 (0.82–1.87)	0.31
Transient ischemic attack	186	237	0.78 (0.64–0.95)	0.01
Myocardial infarction	198	193	1.02 (0.84–1.25)	0.82
Coronary revascularization	388	371	1.04 (0.91–1.20)	0.55
Death from cardiovascular cause	120	125	0.96 (0.74–1.23)	0.73

CI, confidence interval.

* Relative risks estimated by Cox proportional hazard models controlled for age and vitamin E and beta carotene treatment assignments.

[†] A major cardiovascular event was defined as a nonfatal myocardial infarction, a nonfatal stroke, or death from cardiovascular cause.

Table 3

Randomized aspirin assignment and risk of vascular events according to migraine and aura status in the Women's Health Study (N=39,757)

	No history of migraine			Migraine with aura			Migraine without aura			Prior migraine			P*
	ASA	PLA	RR [†] (95% CI)	ASA	PLA	RR [†] (95% CI)	ASA	PLA	RR [†] (95% CI)	ASA	PLA	RR [†] (95% CI)	
No.	16,241	16,186		1029	1030		1559	1556		1116	1040		
Major CVD [‡]	384	427	0.88 (0.77–1.01)	40	26	1.45 (0.88–2.38)	26	30	0.83 (0.49–1.41)	27	38	0.78 (0.48–1.28)	0.26
Stroke	179	216	0.81 (0.67–0.99)	14	20	0.68 (0.34–1.36)	12	17	0.68 (0.33–1.43)	16	13	1.34 (0.64–2.79)	0.48
Ischemic stroke	135	179	0.74 (0.59–0.92)	12	15	0.77 (0.36–1.65)	11	15	0.70 (0.32–1.53)	12	12	1.09 (0.49–2.44)	0.82
Hemorrhagic stroke	44	33	1.31 (0.84–2.06)	2	5	0.44 (0.08–2.29)	1	2	0.54 (0.05–6.03)	4	1	4.17 (0.46–37.62)	0.23
TIA	157	191	0.81 (0.66–1.00)	10	11	0.92 (0.39–2.19)	4	20	0.19 (0.07–0.57)	15	15	1.06 (0.52–2.17)	0.02
Myocardial infarction	159	159	0.98 (0.79–1.23)	20	5	3.72 (1.39–9.95)	11	12	0.88 (0.39–2.01)	8	17	0.52 (0.22–1.20)	0.01
Coronary revascularization	309	294	1.04 (0.88–1.22)	32	19	1.55 (0.87–2.74)	23	22	1.02 (0.57–1.83)	24	36	0.73 (0.44–1.23)	0.26
CVD death	102	107	0.94 (0.71–1.23)	9	4	2.14 (0.65–7.08)	5	3	1.59 (0.38–6.66)	4	11	0.40 (0.13–1.27)	0.20

ASA, aspirin; PLA, placebo; RR, relative risk; CI, confidence interval; CVD, cardiovascular disease; TIA, transient ischemic attack.

* P for interaction from a likelihood ratio test with 3 *df*. P > 0.05 indicate that the effect of aspirin on cardiovascular disease events is not significantly different in migraine subgroups compared to the entire cohort.

[†] Relative risks estimated by Cox proportional hazard models controlled for age, history of hypertension, systolic blood pressure, body mass index of 30 kg/m² or more, and vitamin E and beta carotene treatment assignments.

[‡] A major CVD was defined as nonfatal stroke, nonfatal myocardial infarction or death from cardiovascular cause.

Age-adjusted absolute risks of vascular disease events per 10,000 women per year, according randomized aspirin and to migraine and migraine aura status in the Women's Health Study.

Table 4

	No history of migraine (n=32,427)		Migraine with aura (n=2059)		Migraine without aura (n=3115)		Prior migraine (n=2156)	
	Aspirin	Placebo	Aspirin	Placebo	Aspirin	Placebo	Aspirin	Placebo
Major cardiovascular event (n=998) *	24.1	27.1	39.9	25.7	16.7	19.7	26.9	35.0
Stroke (n=487)	11.2	13.6	13.9	19.7	7.8	11.1	15.8	12.1
Ischemic (n=391)	8.4	11.3	11.9	14.8	7.1	9.9	11.7	11.1
Hemorrhagic (n=92)	2.7	2.1	2.0	4.9	0.6	1.3	4.1	1.0
Transient ischemic attack (n=423)	9.8	12.0	9.9	11.3	2.5	13.1	15.0	14.2
Myocardial infarction (n=391)	9.9	10.0	19.8	4.8	7.0	7.9	8.0	15.4
Coronary revascularization (n=759)	19.4	18.5	32.2	19.0	14.7	14.4	23.5	33.1
Death from cardiovascular cause (n=245)	6.4	6.7	8.8	4.0	3.2	1.9	3.9	9.9

* A major CVD was defined as nonfatal stroke, nonfatal myocardial infarction or death from cardiovascular cause.