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CLINICAL RESEARCH STUDY

# Migraines, Angiographic Coronary Artery Disease and Cardiovascular Outcomes in Women

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## ABSTRACT

**PURPOSE:** There are conflicting data regarding the association between migraines and cardiovascular events. We evaluated the relationship between migraine headaches, angiographic coronary artery disease, and cardiovascular events in women.

**SUBJECTS AND METHODS:** The Women's Ischemia Syndrome Evaluation (WISE) study is a National Heart, Lung and Blood Institute (NHLBI)-sponsored prospective, multicenter study aiming to improve ischemia evaluation in women. A total of 944 women presenting with chest pain or symptoms suggestive of myocardial ischemia were enrolled and underwent complete demographic, medical, and psychosocial history, physical examination, and coronary angiography testing. A smaller subset of 905 women, representing a mean age of 58 years, answered questions regarding a history of migraines. We prospectively followed 873 women for 4.4 years for cardiovascular events and all-cause mortality.

**RESULTS:** Women reporting a history of migraines ( $n = 220$ ) had lower angiographic coronary severity scores, and less severe ( $\geq 70\%$  luminal stenosis) angiographic coronary artery disease compared to women without a history of migraines ( $n = 685$ ). These differences remained statistically significant after adjustment for age and other important cardiac risk factors. On prospective follow-up of a median of 4.4 years, women with a history of migraines were not more likely to have a cardiovascular event (hazard ratio [HR] 1.2; 95% confidence interval [CI], 0.93-1.58) and migraines did not predict all-cause mortality (HR 0.96; 95% CI, 0.49-1.99).

**CONCLUSION:** Among women undergoing coronary angiography for suspected ischemia, those reporting migraines had less severe angiographic coronary artery disease. We could not support an association between migraines and cardiovascular events or death. Further research studying the common pathophysiology underlying migraines and cardiovascular disease is warranted. © 2006 Elsevier Inc. All rights reserved.

**KEYWORDS:** Migraines; Coronary artery disease; Cardiovascular events

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Migraine headaches are a common condition affecting approximately 13% of the population<sup>1,2</sup> and cause substantial impairment in daily activity and productivity. The underlying pathophysiology of migraines is not fully understood, and recent findings have suggested that deregulation of the sympathetic nervous system and alterations in the craniovascular circuitry may play an important role.<sup>3</sup> Migraines also have been linked with vasomotor disorders like Raynauds and Prinzmetal's angina, lending support to a vascular etiology<sup>4-7</sup> and to the possibility of an association between migraine headaches and cardiovascular events, like angina, myocardial infarction and stroke.

The data regarding the true relationship between a history of migraine headaches and angina, and migraine headaches and cardiovascular events such as myocardial infarction and stroke are conflicting. While multiple population-based studies have found that patients with migraine headaches are more likely to have chest pain symptoms,<sup>8-11</sup> the reported association between migraine headaches and major cardiovascular events has been inconsistent. One large study observed a relationship between migraine headaches and cardiovascular events in a community-based study of 3654 Australian men and women, and noted that subjects with migraine headaches were twice as likely to have a self-reported history of myocardial infarction.<sup>12</sup> Conversely, findings from the more recent prospective Nurses and Physicians Health Studies failed to show an association between migraine headaches and verified cardiovascular events, including angina and myocardial infarction.<sup>13</sup> A possible explanation for these discrepant findings may include the reliance on self-reported cardiovascular events, as studies using verified events data have consistently highlighted an absence of an association between migraine headaches and cardiovascular events.<sup>14</sup> To date, there are no published data evaluating the association between migraine headaches and angiographic coronary artery disease.

Our study examines the relationship between migraine headaches, angiographic coronary artery disease, and cardiovascular outcomes in women enrolled in the National Heart Lung and Blood Institute (NHLBI)-sponsored Women's Ischemia Syndrome Evaluation (WISE) study who underwent coronary angiography for suspected myocardial ischemia. We evaluated the women with respect to a history of migraine headaches and quantitative coronary angiography, and prospectively followed them for 4.4 years for cardiovascular outcomes and all-cause mortality.

## METHODS

The WISE study is a 4-center study that aims to improve the diagnostic reliability of cardiovascular testing in the evaluation of ischemic heart disease in women. Women with chest pain symptoms or suspected ischemia underwent an initial evaluation that included coronary angiography, as well as collection of demographic, medical history, psychosocial and symptom data, as described previously.<sup>15</sup> A total of 944 women underwent a full medical history, physical examination, psychosocial evaluation, coronary artery disease risk factor assessment, and multiple serum tests analysis. Of the 944 women, 905 completed baseline information pertaining to migraine headaches, and 873 were prospectively followed for cardiovascular events for a median of 4.4 years.

### Migraine Headaches and Symptom Reporting

Women were asked about a history of migraine headaches using a self-report questionnaire with possible responses of "yes," "no" or "unknown." Chest pain symptoms were assessed using questions about pain or discomfort

above the waist in the last 12 months. The quality of chest pain was further characterized as typical angina, atypical angina, or nonanginal chest pain. Chest pain symptoms were present in 94% of all women. Women were also asked about vasomotor symptoms related to perimenopause and menopause to assess overall symptom-reporting behavior.

### Cardiac Risk Factors and Coronary Angiography

Cardiac risk assessment was done using a self-report questionnaire inquiring about history of diabetes, dyslipidemia, hypertension, and family history of coronary artery disease and other cardiac risk factors. The 10-year risk of myocardial infarction was calculated using the Atherosclerosis Risk Factors in Communities (ARIC) and Adult Treatment Panel (ATP) III guidelines.<sup>16-18</sup>

All coronary angiograms obtained at enrollment were quantitatively and qualitatively evaluated for the presence and extent of coronary artery disease by the WISE angiographic core lab as previously described.<sup>19,20</sup> Severe coronary artery disease was defined as  $\geq 70\%$  stenosis in  $\geq 1$  epicardial coronary artery. The WISE coronary artery disease severity score was calculated based on percent of

## CLINICAL SIGNIFICANCE

- The 'vascular theory' behind migraine headaches suggests a possible relationship between migraine headaches and cardiovascular events such as angina, myocardial infarction and stroke. However, studies have shown that patients with migraine headaches may have chest pain symptoms without being at increased risk for cardiovascular events.
- In this study, women reporting migraines were found to have less angiographic coronary artery disease. This explains the absence of a direct relationship between migraine headaches and cardiovascular events.
- Patients with migraine headaches may be more prone to non-atherosclerosis-mediated chest pain.

luminal stenosis, location of each stenosis, and presence of collaterals as previously described.<sup>19,20</sup>

## Cardiovascular Outcomes

Follow-up was conducted by telephone interview at 6 weeks and annually thereafter. Follow-up consisted of a scripted interview by an experienced nurse or physician. Each patient was asked about occurrence of a cardiovascular event, hospitalizations, repeat angiograms, revascularization procedures, or change in symptoms. The primary outcome of cardiovascular event included fatal and nonfatal myocardial infarction, congestive heart failure, stroke, vascular event, hospitalization for angina and coronary revascularization procedure. A vascular event was defined as any vascular-related hospitalization, including peripheral thrombosis or carotid endarterectomy but excluding revascularization procedures like coronary artery by-pass grafting or percutaneous transluminal coronary angioplasty. We performed secondary analyses of individual endpoints, including angina hospitalization, myocardial infarction and death. When a major cardiovascular event was identified, the referring physician was contacted for confirmation, dates and documentation. In the event of a death, a death certificate was obtained to ascertain cause of death.

## STATISTICAL ANALYSIS

Data are presented as means  $\pm$  standard deviation for continuous variables and percentages for categorical variables. Differences in continuous baseline characteristics by history of migraine headaches were assessed by *t* tests or Wilcoxon rank sum tests, where appropriate. The chi-squared statistic was computed for categorical comparisons of baseline characteristics by the presence or absence of migraine headaches; Fisher's exact tests were utilized when expected cell counts were  $<5$ . Because of a strong relationship between migraine headaches and age, all analyses included an adjustment for age using logistic regression. Stepwise logistic regression was used to model angiographic coronary artery disease as a function of migraine headaches and other significant coronary risk factors including hypertension, tobacco use, family history of coronary artery disease, body mass index and race. Stepwise Cox proportional hazards regression was used to model cardiovascular outcomes as a function of migraine headaches and other significant cardiac risk factors. *P* values  $<.05$  were considered statistically significant. All analyses were performed using the SAS 8.02 software (SAS Institute Inc., Cary, NC).

## RESULTS

The mean age of the women was 58 years and the majority had at least one cardiac risk factor. Representation of minorities was 18%, with 17% being African American. The overall prevalence of a history of migraine headaches was 24%. Women reporting migraines were younger, were less likely to be postmenopausal, and had lower incomes compared to women without a history of

migraines. Women with migraines were more likely to have a history of depression and hysterectomy than women without migraines (Table 1).

## History of Migraines, Coronary Risk Factors and Angiographic Coronary Artery Disease

Significant differences between the 2 groups included a lower prevalence of diabetes, dyslipidemia and the metabolic syndrome in women with migraine headaches. Women reporting migraine headaches were less likely to be on aspirin or a lipid-lowering agent when compared to women without migraines. With respect to global risk factor indices, including the ARIC and ATP III global cardiac risk scores (Table 1), women with migraines had lower overall risk scores in comparison to women without migraine headaches.

Women reporting a history of migraine headaches had less severe ( $\geq 70\%$  stenosis) coronary artery disease and lower coronary severity scores compared to women without a history of migraine headaches (Table 2).

## Symptom Reporting and Prior Stress Testing

Women with a history of migraines were equally likely to have typical and atypical angina symptoms when compared to women without a history of migraines. Menopausal symptoms in peri-menopausal and postmenopausal women, with and without migraine headaches, were also not significantly different (Table 3). A subgroup of patients also were evaluated with respect to stress testing before cardiac catheterization, and women with a history of migraines were just as likely to have undergone a noninvasive stress test before angiography as women without a history of migraines.

## Cardiovascular Outcomes and Death

Women with migraine headaches were not more likely to have a cardiovascular event compared to women without migraines even after multivariable adjustment for significant risk factors (Table 4) between the 2 groups. Similarly, a history of migraine headaches did not predict all-cause mortality (Table 4).

## DISCUSSION

Although previous reports have demonstrated an inconsistent association between a history of migraine headaches and cardiovascular events, migraine headaches have not been studied with respect to angiographic coronary artery disease. Our findings suggest that among women undergoing coronary angiography for suspected myocardial ischemia, those with a history of migraine headaches have less severe coronary artery disease on angiography and lower coronary artery severity scores compared with women who did not report migraine headaches. This difference remained significant after adjustment for age and other significant cardiac risk factors.

**Table 1** Baseline Variables by History of Migraine Status

Variable	History of Migraines n = 220	No History of Migraines n = 685	P Value
<b>Demographic variables</b>			
Age (years) (± SD)	54 ± 11	59 ± 12	<.01
Postmenopausal (%)	67	78	<.01
Non-White race (%)	21	18	.24
Income ≥35 000 (%)	33	41	.04
Education > high school (%)	77	82	.07
History of hysterectomy (%)	63	50	<.01
History of depression (%)	37	20	<.01
<b>CVD risk factors</b>			
Current smoker (%)	25	19	.07
Family history of CAD (%)	71	65	.08
Diabetes mellitus (%)	19	27	.03
Dyslipidemia (%)	49	57	.04
Hypertension (%)	56	59	.53
Obese (BMI ≥30) (%)	42	41	.92
Metabolic syndrome (%)	40	49	.02
<b>Current medication use</b>			
Lipid lowering medication (%)	17	33	<.01
Antidepressant or other psychotropic medications (%)	38	28	<.01
Aspirin (%)	53	62	.01
Beta-blockers (%)	33	41	.06
ACE inhibitors (%)	24	26	.47
<b>Cardiac risk scores</b>			
ARIC risk score [median (IQR)]	3.0 (2-8)	4.0 (2-9)	<.01
ATP III risk score [median (IQR)]	2.0 (1-5)	3.0 (1-6)	<.01

CVD = cardiovascular disease; CAD = coronary artery disease; BMI = body mass index; ACE = angiotensin-converting enzyme; ARIC = Atherosclerosis Risk Factors in Communities; ATP III = Adult Treatment Panel.

With respect to migraine headaches and angina, several studies, including a recent ARIC publication,<sup>14</sup> showed a higher prevalence of Rose angina<sup>21</sup> in patients with migraine headaches without an associated increased risk for cardiovascular events. This would suggest that women with migraines may be more prone to non-atherosclerosis-mediated chest pain symptoms. In support, reports have shown that those who suffer from migraine headaches have lower overall pain thresholds compared with normal controls.<sup>8</sup> However, in our study, patients

with a history of migraine headaches did not report more typical or atypical angina symptoms. It is possible that the high percentage of patients with chest pain (94%) in our cohort may not have allowed us to effectively study this association.

We also explored a variety of confounder variables that could potentially explain the inverse association between a history of migraine headaches and angiographic coronary artery disease. Firstly, women with migraine headaches were younger and had lower global cardiac risk scores, including ARIC and ATP scores, reflecting a lower overall risk for coronary artery disease. However, after adjustment for age only, the ARIC and ATP risk

**Table 2** Angiographic Coronary Artery Disease and CAD Severity Score by History of Migraine Status

Variable	History of Migraines n = 220	No History of Migraines n = 685	P Value	Adjusted P Value*
CAD ≥70% stenosis (%)	13	28	<.01	.01
CAD severity score (median)	6.25	8.88	<.01	.03

CAD = coronary artery disease.

\*Adjusted for age, history of diabetes, body mass index, history of smoking, family history of coronary artery disease, race, waist-hip ratio, aspirin use, current smoking, and dyslipidemia.

**Table 3** Symptom Reporting by History of Migraine Status

	History of Migraines n = 220	No History of Migraines n = 685	P Value
Typical angina (%)	33	32	.77
Atypical angina (%)	39	38	.77
Nonanginal chest pain (%)	23	22	.89
Asymptomatic (%)	6	8	.21
Menopausal symptoms (%)	73	66	.11
Prior stress test (%)	43	47	.22

**Table 4** CV Outcomes by History of Migraine Status

	Age		Migraine Headaches	
	HR (95% CI)	P Value	Adjusted HR (95% CI)*	Adjusted P Value*
Death	1.05 (1.03-1.07)	<.01	0.96 (0.49-1.99)	.91
Death or MI	1.03 (1.02-1.05)	<.02	1.10 (0.60-1.91)	.86
Angina hospitalization	1.00 (0.99-1.01)	.42	1.27 (0.93-1.75)	.14
PTCA	1.02 (1.01-1.04)	<.01	0.80 (0.50-1.35)	.39
CABG	1.019 (1.00-1.04)	.09	0.76 (0.33-1.77)	.53
PTCA or CABG	1.03 (1.00-1.04)	<.01	0.81 (0.50-1.30)	.39
CV event	1.01 (1.00-1.02)	<.05	1.21 (0.93-1.58)	.15
CV death	1.00 (0.97-1.03)	.87	1.16 (0.20-6.7)	.87

MI = myocardial infarction, PTCA = percutaneous transluminal coronary angioplasty, CABG = coronary artery bypass grafting.

\*Adjusted for age, history of diabetes, body mass index, history of smoking, family history of coronary artery disease, race, waist-hip ratio, aspirin use, current smoking, dyslipidemia, and CAD severity score.

scores did not significantly differ between the 2 groups, and therefore, the lack of angiographic coronary artery disease could not be explained simply by less overall cardiac risk in patients with migraine headaches.

Another possibility could be related to symptom reporting, where women with migraine headaches might more frequently report symptoms of chest pain and other symptoms, and therefore, more frequently undergo coronary angiography at a relatively lower level of coronary artery disease risk. In our cohort, women with a history of migraine headaches did not differ with respect to coronary artery disease risk profiles after age adjustment and were not more likely to report chest pain or other symptoms (Table 3). Moreover, diagnostic evaluation leading to coronary angiography demonstrated that both groups were similar in terms of noninvasive stress testing for coronary artery disease before catheterization. The clinical indication for cardiac catheterization appeared to be similar in the 2 groups, and we were unable to identify a selection bias.

Potential explanations for the inverse association between migraine headaches and angiographic coronary artery disease remain speculative. Studies have suggested, and it is plausible, that women with migraine headaches have a vasospastic disorder mediating chest pain symptoms.<sup>8</sup> This could result in findings of less angiographic coronary artery disease in these patients.

Our current findings help provide a pathophysiologic explanation for results from the Women's and Physician's Health Studies that showed no association between a history of migraines and risk of subsequent major or total cardiovascular events in men or women.<sup>13</sup> Notably, in the Women's and Physician's Health Studies, there were fewer overall cardiovascular events and deaths in the migraine group consistent with our findings of less angiographic coronary artery disease in this group. Additionally, in the recent ARIC study publication, which evaluated an association between migraine headaches, Rose angina and cardiovascular events, a modest but significant decrease in the prevalence of cardiovascular

events was noted in patients with headaches.<sup>14</sup> Our current results expand on this observation and suggest that these findings may be explained by lesser degree of severe angiographic coronary artery disease in this group.

Notably, in our patient cohort, we did not observe a significantly lower cardiovascular event rate despite having less angiographic coronary artery disease and lower overall coronary artery disease severity among the women with migraines. A potential explanation for this could include inadequate follow-up time in a group of women who were younger and at relatively low risk. However, it is also possible that women with migraine headaches may suffer from vascular endothelial dysfunction, which we have demonstrated in the WISE to have an adverse impact on morbidity and mortality in women with chest pain in the setting of nonobstructive angiographic coronary artery disease (Cardiac Syndrome X).<sup>22</sup>

## LIMITATIONS

The current results are limited because we did not use the more rigorous International Headache Society criteria<sup>23</sup> for diagnosing migraine headaches. Many major studies of migraine headaches have used modified International Headache Society criteria or self-report questionnaires. The validity of self-assessment of migraines was recently reported in 23,564 patients where it was noted that patients who self-reported migraine were 3 times more likely to meet International Headache Society criteria than those classifying their headaches as other than migraines.<sup>24</sup> Another limitation was the absence of further classification of migraine with or without aura. Patients with migraine with aura have been shown to be a group at slightly increased risk for vascular events like ischemic stroke.<sup>25</sup> Our study was unable to explore this association. In addition, our study population was restricted to select women who were undergoing angiography for suspected myocardial ischemia, limiting our ability to extrapolate these results to the general population.

## CONCLUSION

Our results demonstrate that among women undergoing coronary angiography for suspected myocardial ischemia, a history of migraine headaches is associated with less angiographic coronary artery disease. Consistent with prior studies, women with a history of migraine headaches did not have more cardiovascular events or death when compared to women without migraine headaches. Further prospective study is needed to better understand the mechanistic relationships between chest pain symptoms, migraine headaches, and cardiovascular events.

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