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ORIGINAL RESEARCH

Aspirin Use and Risk of Atrial Fibrillation in the Physicians' Health Study

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***Background*—**Inflammatory processes have been associated with an increased risk of atrial fibrillation (AF), potentially allowing for preventive therapy by anti-inflammatory agents such as aspirin. However, the effect of chronic aspirin on the incidence of AF has not been evaluated in a prospective cohort followed for an extended period.

***Methods and Results*—**This study was comprised of a prospective cohort of 23 480 male participants of the Physicians' Health Study. Aspirin intake and covariates were estimated using self-reported questionnaires. Incident AF was ascertained through yearly follow-up questionnaires. Cox's regression, with adjustment for multiple covariates, was used to estimate relative risk of AF. Average age at baseline was 65.1±8.9 years. During a mean follow-up of 10.0 years, 2820 cases of AF were reported. Age-standardized incidence rates were 12.6, 11.1, 12.7, 11.3, 15.8, and 13.8/1000 person-years for people reporting baseline aspirin intake of 0, <14 days per year, 14 to 30 days per year, 30 to 120 days per year, 121 to 180 days per year, and >180 days per year, respectively. Multivariable adjusted hazard ratios (95% confidence interval) for incident AF were 1.00 (reference), 0.88 (0.76 to 1.02), 0.93 (0.76 to 1.14), 0.96 (0.80 to 1.14), 1.07 (0.80 to 1.14), and 1.04 (0.94 to 1.15) across consecutive categories of aspirin intake. Analysis of the data using time-varying Cox's regression model to update aspirin intake over time showed similar results.

***Conclusions*—**In a large cohort of males followed for a long period, we did not find any association between aspirin use and incident AF. **(*J Am Heart Assoc*. 2014;3:e000763 doi: 10.1161/JAHA.113.000763)**

Key Words: aspirin • atrial fibrillation • epidemiology • risk factors

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting ≈2.3 million people in the United States and 4.5 million in the European Union.[1] AF is costly, because increased risk of stroke associated with it necessitates expensive, labor-intensive anticoagulation in many patients diagnosed with this arrhythmia. Despite the prevalence and cost of AF, there are no known effective strategies available for the prevention of AF.

Although the pathogenesis of AF is not completely understood, and is believed to be multifactorial,[2] studies have demonstrated increased levels of biochemical markers of inflammation in patients with AF.[3,4] Subjects with AF have increased levels of C-reactive protein and interleukin (IL)-6, when compared to the general population.[3] Several non-antiarrhythmic medications, such as statins, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, aldosterone, and polyunsaturated fatty acids, have been shown to play a role in prevention of AF in certain subgroups of patients.[5] These medications have anti-inflammatory and anti-oxidant properties, which are thought to be responsible for their anti-arrhythmic potential.[5] Aspirin exhibits anti-inflammatory activity by its effects on cyclooxygenase (COX) activity, which is linked to inflammation[6] as well as by inhibiting IL-4 and nuclear factor kappa B gene expression in non-COX-dependent pathways.[7]

Because of these effects of aspirin on inflammatory cytokines and the association between AF and markers of inflammation, aspirin has been hypothesized as potentially having prophylactic properties for AF. However, few

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researchers have evaluated this hypothesis in a large, prospective cohort with long-term follow-up. Therefore, we aimed to examine the relationship between intake of aspirin and incidence of AF in a large, prospective cohort of men.

Methods

Study Population

Data were obtained from the Physicians' Health Study (PHS). Details of the methods of the PHS have been described elsewhere.[8–10] Briefly, PHS I began in 1982 as a randomized, double-blind, placebo-controlled trial of aspirin and beta-carotene in 22 071 U.S. male physicians 40 to 84 years of age with no history of myocardial infarction (MI), stroke, transient ischemic attack, or cancer at the time of randomization. The study was designed to test the effects of aspirin (325 mg every other day) and beta-carotene in the primary prevention of cardiovascular disease (CVD) and cancer. PHS II started in 1997 and was a randomized trial of efficacy of beta-carotene, vitamin C, vitamin E, and a multivitamin on CVD and cancer risk in 7641 PHS I physicians and 7000 newly recruited male physicians. At PHS II enrollment, all subjects received a baseline questionnaire, which included the question "Have you ever been diagnosed with atrial fibrillation?" All PHS subjects have been followed prospectively, using annual mailed health questionnaires to collect self-reported data, including new cancer and CVD diagnoses. Although AF was not one of the primary endpoints of the trial, we prospectively collected data on incident AF starting in 1998. Current analysis focused on the PHS II time period because of better and regular ascertainment of incident AF using annual follow-up questionnaires. During this time period, the study population included three categories: newly enrolled PHS II participants; participants who enrolled in PHS II after completion of PHS I; and participants from PHS I who were not included in PHS II but continued to be followed over time. All three groups were evaluated for inclusion in the current study, for a total of 26 395 participants. Of these, 2128 participants were excluded because of prevalent AF at baseline, and 787 were excluded because they did not provide data on aspirin intake at baseline. The remaining 23 480 participants were analyzed. Each participant singed an informed consent and the institutional review board at Brigham and Women's Hospital (Boston, MA) approved the study protocol.

Outcome

Self-reported AF was assessed annually by follow-up questionnaires. These self-reports of AF have been validated in another study conducted in the same cohort using a more detailed questionnaire on the diagnosis of AF and review of medical records.[8,11]

Other Variables

Data on demographics, including race and age, anthropometrics, including age and body mass index (BMI), comorbidities, such as coronary heart disease (CHD), congestive heart failure (CHF), hypertension (HTN), diabetes, left ventricular hypertrophy (LVH), and valvular heart disease, and lifestyle factors, including physical activity, smoking, alcohol consumption, as well as use of nonsteroidal anti-inflammatory drugs (NSAIDs), were assessed by questionnaires administered at baseline. Alcohol consumption was classified as none, 1 to 3 drinks per month, 1 to 6 drinks per week, and 7 or more drinks per week. Smoking was classified as never, past, and current smokers. Physical activity was classified as exercising to sweat 1 or more times per week versus <1 per week. Diagnosis of diabetes was self-reported and validated in a subsample.[12] HTN was defined as self-reported diagnosis of HTN, reported blood pressure of blood pressure >140/90 mm Hg, or use of antihypertensive medications at baseline. Subjects who reported coronary artery bypass graft surgery or MI before PHS II enrollment were deemed as having CHD. Ascertainment of CHF in PHS has been published elsewhere.[13]

Aspirin Intake

At start of PHS I in 1982, subjects were randomized to receive either aspirin or placebo. The randomized aspirin administration was terminated in January 1988. The second stage (aspirin intake based on participants' preference) continued thereafter. Nontrial aspirin use was assessed using annual questionnaires. At enrollment in the PHS II, and on annual follow-up questionnaires, participants were asked, "Over the past 12 months, on approximately how many days did you take aspirin or medication containing aspirin?" Possible responses included 0, 1 to 13 days, 14 to 30 days, 31 to 60 days, 61 to 90 days, 91 to 120 days, 121 to 180 days, and 181+ days. Actual dose of aspirin was not ascertained.

Statistical Analysis

Because of the small number of AF events in the aspirin categories of 31 to 60 days per year (n=56 events), 61 to 90 days per year (n=48 events), and 91 to 120 days per year (n=57 events), we combined these three adjacent categories to obtain stable estimates of effect. We finally classified each subject into 1 of the 6 categories based on baseline aspirin intake: none, <14 days per year, 14 to 30 days per year, 31 to 120 days per year, 121 to 180 days per year, and

>180 days per year. Within each aspirin category, we calculated age-standardized incident rates using the person-time distribution across 5-year age categories (<55, 55 to 59, 60 to 64, 65 to 69, 70 to 74, 75 to 79, 80 to 84, and 85+) and weighting by the 2000 U.S. population.

We computed follow-up person-time from baseline aspirin assessment (PHS II enrollment) until the first occurrence of AF for incident AF cases or censoring time for subjects that did not develop AF during follow-up (these subjects were censored at their time of death or at the time of receipt of last follow-up questionnaire). Baseline characteristics were compared across the categories of reported aspirin use. For all categorical variables except smoking, we created indicator variables for missing observations.

We used Cox's proportional hazard models to compute multivariable adjusted hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) using participants in the lowest category of aspirin intake as the reference group. Proportional hazard assumptions were tested by including an interaction term with logarithmic-transformed person-time of follow-up in Cox's regression model ($P>0.05$).

First, we adjusted for age alone (continuous and quadratic), then we added variables to the model based on their potential to be confounders of the relation between aspirin use and AF. In model 1, we adjusted for age (continuous and quadratic), BMI (continuous), alcohol intake (none, 1 to 3 drinks per month, 1 to 6 drinks per week, and 7 or more drinks per week), exercise to sweat at least once a week, smoking (never, past, and current), and PHS I randomization to aspirin (with indicator variable to retain newly recruited subjects). Model 2 also controlled for comorbidities, including diabetes, NSAIDs, valvular heart disease, LVH, and HTN.

In secondary analysis, we repeated main analysis by updating aspirin use over time in a time-dependent multivariable adjusted Cox model, updating aspirin use annually. We imputed data from the previous 2 years for individuals with missing data on aspirin use at a given time period. Finally, we used logistic regression to compute odds ratios (ORs) with corresponding 95% CIs for participants randomized only to aspirin or placebo (during the PHS I time period). Though AF information for these subjects was available, a lack of exact time of AF occurrence before 1998 prevented us from using Cox's regression.

All analyses were conducted using SAS software (version 9.2; (SAS Institute Inc., Cary NC). Significance level was set at 0.05.

Results

Table 1 shows the baseline demographics of 23 480 subjects according to categories of aspirin intake. Mean age of the study participants was 65.1±8.9 years. Among the participants reporting aspirin intake, 4956 reported no aspirin intake, 2898 took aspirin <14 days per year, 1110 took 14 to 30 days per year, 1494 took 30 to 120 days per year, 2162 took 121 to 180 days per year, and 10 860 took >180 days per year (Table 1).

Frequent aspirin intake was associated with slightly, but statistically significantly, older age and higher BMI (Table 1). As expected, those who took aspirin for more than 180 days per year had significantly higher prevalence of major comorbidities, including CHD, diabetes, HTN, and LVH. Frequent aspirin intake was not associated with significantly higher prevalence of CHF, probably because of infrequent CHF diagnosis in our study population (1.3%).

A median follow-up for newly enrolled PHS II participants was 10.9 (SD, 10.5 to 11.2) years, 13.3 (SD, 9.5 to 13.6) years for participants who enrolled in PHS II after participating in PHS I, and 11.7 (SD, 6.7 to 12.0) years for participants from PHS I who were not enrolled in PHS II. Total mean follow-up was 10.0 years, during which 2820 cases of AF occurred.

Age-adjusted incidence rates were 12.6, 11.1, 12.7, 11.3, 15.8, and 13.8/1000 person-years from the lowest to the highest category of aspirin intake (none, <14 days per year, 14 to 30 days per year, 30 to 120 days per year, 121 to 180 days per year, and >180 days per year), respectively (Table 2). There was no statistically significant association between aspirin intake and incident AF. Multivariable adjusted HRs (95% CI) for incident AF were 1.00 (reference), 0.88 (0.76 to 1.02), 0.93 (0.76 to 1.14), 0.96 (0.80 to 1.14), 1.07 (0.80 to 1.14), and 1.04 (0.94 to 1.15) from the lowest to the highest category of aspirin intake (Table 2). The findings did not change significantly when subjects with CHD and CHF at baseline were excluded from the analysis.

The use of the time-dependent Cox model with updated aspirin use over time did not alter the results (OR [95% CI] were 1.00 [reference], 0.94 [0.81 to 1.10], 0.97 [0.77 to 1.21], 1.04 [0.86 to 1.25], 0.93 [0.79 to 1.11], and 1.10 [0.99 to 1.21] from the lowest to the highest category of aspirin intake). Furthermore, when assessing PHS I subjects during the PHS I study period, intervention with low-dose aspirin was not associated with the odds of AF when compared to placebo (OR [95% CI], 1.08 [0.85 to 1.38]).

Discussion

Our findings did not support an association between cumulative aspirin use and incident AF among U.S. male physicians. These findings persisted after updating aspirin use over time. To the best of our knowledge, this is the first large, prospective study to assess the association of long-term aspirin intake with incidence of AF.

Table 1. Baseline Characteristics of 23 480 Subjects in the Physicians' Health Study*

	Aspirin Use (Days/Year)						Total Sample	*P* for Linear Trend
	0	1 to 13	14 to 30	31 to 120	121 to 180	181+		
N, %	4956 (21.1)	2898 (12.3)	1110 (4.7)	1494 (6.4)	2162 (9.2)	10 860 (46.3)	23 480	
Mean age±SD	64.6±9.7	62.6±8.5	64.0±8.7	64.1±8.8	66.5±8.2	66.0±8.6	65.1±8.9	<0.0001
Age-adjusted BMI±SD	25.6±0.1	25.7±0.1	25.6±0.2	25.7±0.2	25.6±0.1	26.0±0.06	25.8±3.4	0.0032
Alcohol								
1 to 3 drinks/month, %	1382 (27.9)	947 (32.7)	391 (35.2)	502 (33.6)	895 (41.4)	4175 (38.4)	8292 (35.3)	<0.0001
1 to 6 drinks/week, %	1814 (36.6)	1167 (40.3)	438 (39.5)	595 (39.8)	839 (38.8)	4010 (36.9)	8863 (37.8)	0.1565
≥7 drinks/week, %	470 (9.5)	237 (8.2)	81 (7.3)	122 (8.2)	95 (4.4)	676 (6.2)	1681 (7.2)	<0.0001
Rare/none, %	1132 (22.8)	509 (17.6)	181 (16.3)	241 (16.1)	312 (14.4)	1791 (16.5)	4166 (17.7)	<0.0001
CHD, %	160 (3.2)	56 (1.9)	43 (3.9)	56 (3.8)	106 (4.9)	1647 (15.2)	2068 (8.8)	<0.0001
CHF, %	83 (1.7)	9 (0.31)	10 (0.90)	15 (1.0)	22 (1.0)	173 (1.6)	312 (1.3)	0.0861
Diabetes, %	328 (6.6)	128 (4.4)	66 (6.0)	80 (5.4)	122 (5.6)	931 (8.6)	1655 (7.1)	<0.0001
Exercise to sweat at least once a week, %	2856 (57.6)	1789 (61.7)	663 (59.7)	907 (60.7)	1374 (63.6)	6584 (60.6)	14 173 (60.6)	0.0144
HTN, %	1938 (39.1)	1001 (34.5)	444 (40.0)	592 (39.6)	1002 46.4)	5478 (50.4)	10 455 (44.5)	<0.0001
LVH, %	68 (1.4)	17 (0.6)	12 (1.1)	10 (0.7)	30 (1.4)	183 (1.7)	320 (1.4)	0.0016
Smoking status								
Never smoked, %	2796 (56.4)	1667 (57.5)	625 (56.3)	851 (57.0)	1098 (50.8)	5494 (50.6)	12 531 (53.4)	<0.0001
Past smoker, %	1951 (39.4)	1114 (38.4)	451 (40.6)	590 (39.5)	987 (45.7)	4934 (45.4)	10 027 (42.7)	<0.0001
Current smoker, %	199 (4.0)	113 (3.9)	33 (3.0)	51 (3.4)	77 (3.6)	423 (3.9)	896 (3.8)	0.8151
H/o VHD, %	79 (1.6)	18 (0.62)	10 (0.90)	15 (1.0)	30 (1.4)	126 (1.2)	278 (1.2)	0.4540

BMI indicates body mass index; CHD, coronary heart disease; CHF, congestive heart failure; HTN, hypertension; LVH, left ventricular hypertrophy.
*Values are given as N (%), mean±SD, or age-adjusted±SE.
The following variables had missing values: BMI, 1; alcohol use, 478; exercise, 217; hypertension, 130; smoking, 26.

Several factors could have lead to this null effect of aspirin intake on incident AF. It is possible that the anti-inflammatory effect of aspirin is not strong enough to produce a noticeable antiarrhythmic response. It is also possible that the inflammatory pathways inhibited by aspirin are not the ones responsible for AF preventing properties of other nonantiarrhythmic medications. Alternatively, inflammatory changes observed in association with AF might not be the cause, but

Table 2. Hazard Ratios (95% CI) for Atrial Fibrillation According to Aspirin Intake in the Physicians' Health Study II

Aspirin Intake (Days/Year)	Cases/ Person-Years	Crude Incidence Rate (1000 Person-Years)	Age-Standardized Incidence Rate (1000 Person-Years)*	HR (95% CI)			
				Unadjusted	Age Adjusted	Model 1†	Model 2‡
0	513/46 998	10.92	12.6	1.0	1.0	1.0	1.0
1 to 13	269/30 027	8.96	11.1	0.82 (0.70 to 0.94)	0.88 (0.76 to 1.03)	0.87 (0.75 to 1.01)	0.89 (0.76 to 1.03)
14 to 30	116/11 381	10.19	12.7	0.92 (0.75 to 1.13)	0.93 (0.76 to 1.13)	0.93 (0.76 to 1.14)	0.93 (0.76 to 1.14)
31 to 120	161/15 229	10.57	11.3	0.96 (0.80 to 1.14)	0.95 (0.80 to 1.14)	0.94 (0.79 to 1.13)	0.96 (0.80 to 1.14)
121 to 180	312/22 450	13.90	15.8	1.25 (1.08 to 1.43)	1.07 (0.93 to 1.23)	1.07 (0.93 to 1.24)	1.08 (0.94 to 1.25)
>180	1449/108 404	13.37	13.8	1.21 (1.10 to 1.34)	1.08 (0.97 to 1.19)	1.05 (0.95 to 1.16)	1.04 (0.94 to 1.16)

BMI indicates body mass index; CI, confidence interval; HR, hazard ratio; LVH, left ventricular hypertrophy; NSAIDs, nonsteroidal anti-inflammatory drugs.
*Age-standardized incident rate using weights from 2000 U.S. population.
†Adjusted for age (continuous and quadratic), BMI (continuous), alcohol intake (none, 1 to 3 drinks per month, 1 to 6 drinks per week, and 7 or more drinks per week), exercise to sweat least once a week (yes/no), smoking (never, past, and current), PHS I aspirin assignment (aspirin, placebo, and PHS II physician).
‡Additional adjustment for diabetes (yes/no), NSAIDs (none, 1 to 13 days, 13 to 180 days, and 181+ days), hypertension (yes/no), valvular heart disease (yes/no), and LVH (yes/no).

rather the result, of AF. An association between aspirin and AF could be complex, depending upon the type of AF, as is the case with other nonantiarrhythmic medications.[5] The design of our study did not allow us to subanalyze the association between aspirin and subtypes of AF.

Our study has several limitations. First, our population consisted of male physicians, mostly Caucasian, who, in general, are more aware of different health risks, thus making it difficult to generalize our findings to other populations and ethnicities. However, several other studies using PHS, that have identified various associations between exposures and cardiovascular outcomes, have subsequently been found to exist in cohorts of women and other ethnic groups as well. Second, incidence of AF may have been under-reported as a result of asymptomatic or undiagnosed AF. However, AF ascertainment by self-report has been previously validated in PHS.[9] Third, because the actual dose of nonrandomized aspirin was not queried, we could only ascertain a relationship between cumulative aspirin intake and incident AF. We could not make any conclusion on the relationship of the daily dose of aspirin use on incident AF.

Our study has several strengths. We have a large sample size, and a long follow-up period, which improves the statistical power to detect smaller effects. We used standardized questionnaires, and we had a homogeneous group of male physicians, who are able to recognize signs and symptoms of AF more so than the general population.

Conclusion

In summary, our study does not provide evidence in support of a significant association between long-term use of aspirin and increased risk of AF among U.S. male physicians. Further studies are warranted in cohorts of women and in different racial/ethnic backgrounds to confirm our findings.

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