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Journal

European Journal of Internal Medicine, 25(3)

ISSN

0953-6205

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Publication Date

2014-03-01

DOI

10.1016/j.ejim.2014.01.013

Peer reviewed

Published in final edited form as:
Eur J Intern Med. 2014 March ; 25(3): 255–258. doi:10.1016/j.ejim.2014.01.013.

Non-steroidal anti-inflammatory drug use and functional outcome from ischemic cerebral events among women

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Abstract

Background—Use of some non-steroidal anti-inflammatory drugs (NSAIDs) has been linked to an increased risk of stroke. However, information on the impact of NSAID use on functional outcomes from stroke is limited.

Methods—Using women enrolled in the Women's Healthy Study who were free of a history of stroke or TIA at baseline, a prospective cohort study was performed to examine the impact of NSAID use on functional outcomes from stroke. Women were classified as NSAID non-user (<11 days of use in the past month), user (≥11 days of use in the past month), and missing (did not answer the question about NSAID use) during each year of the study. Possible functional outcomes were TIA or ischemic stroke with modified Rankin scale (mRS) score of 0 to1, 2 to 3, or 4 to 6.

Results—After 15.7 mean years of follow-up, 702 TIAs, 292 ischemic strokes with mRS 0-1, 233 ischemic strokes with mRS 2-3 and 98 ischemic strokes with mRS 4-6 occurred. Compared to women who were NSAID non-users, women who were NSAID users had multivariable-adjusted (95% CI) of 1.00 (0.77, 1.29) for TIA, 1.48 (1.04, 2.10) for mRS 0-1, 0.83 (0.52, 1.33) for mRS 2-3, and 1.33 (0.68, 2.59) for mRS 4-6.

Conclusion—Results from this large cohort study suggest than NSAID use may be associated with an increased risk of ischemic stroke with mild functional outcome.

Keywords

epidemiology; stroke; non-steroidal anti-inflammatory drugs

Several studies have examined whether non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with an increased risk of cardiovascular events, including stroke. A meta-analysis of 26 randomized controlled trials showed that naproxen, ibuprofen, diclofenac, celecoxib, etoricoxib, rofecoxib and lumiraccoxib were associated with an

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The authors have no relevant disclosures.

increased risk of stroke compared with placebo although this increase in risk was only statistically significant for diclofenac and lumiracoxib (1). A prospective cohort study among healthy individuals showed that diclofenac use was associated with a significantly increased risk of stroke (2). However, a cohort study among Medicaid enrollees found a significantly increased risk of stroke among rofecoxib and valdecoxib users, but not among diclfenac, celecoxib, ibuprofen, naproxen or indomethacin users (3). In population of Australian veterans, incident use of any NSAID was associated with an increased the risk of hospitalization for a stroke (4).

While several studies have examined the association between non-aspirin NSAID use and risk of stroke, little information exists on the impact non-aspirin NSAID use may have on functional outcomes from stroke in initially healthy populations. Determining if NSAID use impacts functional outcomes from stroke may help inform decisions about NSAID usage in populations without a history of stroke. For example, if the risk of stroke is low, but the risk of a poor functional outcome is high, more caution when prescribing non-aspirin NSAIDs might be warranted.

Using data from a large prospective cohort study, we examined the association between non-aspirin NSAID use and functional outcomes from stroke.

Methods

The Women's Health Study (WHS) was a large, randomized clinical trial designed to test the effects of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer, respectively. The design, methods, and main results have been described previously (5–7). At the start of the WHS (1993–1996), 39,876 US female health professional aged ≥45 years without a history of cardiovascular disease, cancer or other major illnesses were randomized to received active aspirin and placebo vitamin E, active vitamin E and placebo aspirin, both active agents or both placebos. After the end of the clinical trial in March 2004, follow-up of the women continued on an observational basis. Twice within the first year of the trial and yearly thereafter, the women were sent questionnaires asking about demographic information, lifestyle characteristics, medical history, and the occurrence of study endpoints (including stroke and transient ischemic attacks (TIAs)).

The WHS was approved by the institutional review board at Brigham and Women's Hospital. All participants provided written informed consent.

Exposure assessment

To be enrolled in the WHS, the women either had to be not currently taking NSAIDs or indicate that they were willing to forego their usage of NSAIDs during the trial. This requirement helped to ensure that at baseline study participants did not have strong indications or contraindications for NSAID use and substantially reduces confounding by indication to use NSAIDs at study entry.

On each yearly follow-up questionnaire (except for the 6th year of observational follow-up), the women were asked "During the past month, on approximately how many days did you take any of the following (do not count your study pills): Nonsteroidal, anti-inflammatory agents (e.g., Motrin, Advil, Nuprin, Naprosyn, Feldene, Mediprin)." Possible response options were: 0, 1–3, 4–10, 11–20 or ≥21 days in the past month. The women's responses to each of the yearly follow-up questionnaires were used to determine their NSAID use for the following year. We imputed NSAID use for the 6th year of observational follow-up using the women's responses from the 5th year of follow-up. We grouped the women into three

different categories of NSAID use at each study time point: non-user (0, 1–3, or 4–10 days of use in the past month); user (11–20 or ≥21 days of use in the past month); and missing (did not answer the question about NSAID use) from study entry until the date of first stroke or TIA event, death, last documented contact, or end of the study, whichever occurred first

Outcome assessment

If a woman reported the occurrence of a TIA or stroke in her yearly questionnaire, we asked for permission to review her medical records. An Endpoints Committee of physicians (including a board-certified vascular neurologist) reviewed the medical records and decided whether or not to confirm cases of TIA or stroke. A TIA was defined as a focal neurologic deficit of sudden or rapid onset and vascular mechanism that resolved within 24 hours. A nonfatal stroke was defined as a focal neurologic deficit of sudden or rapid onset and vascular mechanism that lasted >24 hours. To confirm cases of fatal stroke, all available sources, including death certificates and hospital records, were reviewed to determine if there was evidence of a cerebrovascular mechanism. The Endpoints Committee classified the strokes according to major subtype (ischemic, hemorrhagic, or unknown) with excellent interobserver agreement (Cohen's κ=0.96) (8). For this analysis, we only used confirmed cases of ischemic stroke. Women who experienced a hemorrhagic stroke or stroke of unknown type will be censored at the time of stroke onset. Additionally, the Endpoints Committee assigned each confirmed stroke was assigned a modified Rankin Scale (mRS) score based on the degree of impairment experienced by the patient at hospital discharge. The seven-point mRS score (0=no symptoms at all; 1=no significant disability despite symptoms; 2=slight disability; 3=moderate disability; 4=moderately severe disability; 5=severe disability; 6=death) (9, 10) was a priori categorized into three levels (0 to 1, 2 to 3, and 4 to 6) for our analyses to avoid possible problems with model convergence due to sparse data an approach consistent with a previous study in the WHS (11). Therefore our possible outcome categories were: no stroke or TIA, TIA, or ischemic stroke with the three possible categories of the mRS. In the event that a woman experienced multiple strokes and/or TIAs, only the first event was used for our analysis.

Confounder scores

Although the participants in the WHS were free of many major medical conditions at baseline, conditions may have developed over the course of the study. To adjust for confounding by other medical conditions that may cause a participant to use NSAIDs and may also increase their risk of a poor functional outcome from stroke, we constructed a modified version of the Charlson comorbidity index (12). We modified the score because we did not have information on renal and liver disease severity. All liver disease was categorized as mild and all renal disease as moderate to severe similar to previous studies (13, 14). Solid tumors which were either localized or metastatic at presentation received a score of 2 and 6, respectively.

We also constructed scores for indications of NSAID use and NSAID side effects or contraindications to adjust for potential confounding by these factors (13). To calculate the score for indications of NSAID we assigned one point for each of the following conditions: migraine, frequent headache (reported ≥3 times), osteoarthritis, inflammatory arthritis, and coronary artery disease. To calculate the score for NSAID side effects or contraindications we assigned one point for each of the following: gastrointestinal bleeding, peptic ulcer, and gastrointestinal symptoms (nausea, vomiting, dyspepsia and dysphagia).

Statistical analysis

We excluded women who reported a history of TIA or stroke at baseline. We used four separate Cox proportional hazards models with time-varying exposure values to determine

the relative risk of experiencing a TIA or ischemic stroke with mRS 0-1, 2-3 or 4-6 compared to not experiencing a TIA or stroke. All other outcome events that were not the outcome of interest for that Cox model were censored at the time of the event. Women contributed person-time from the receipt of the baseline questionnaire until the date of first stroke or TIA event, death, last documented contact, or end of the study, whichever occurred first. Exposure status was updated on a yearly basis based on responses to yearly questionnaires. To test the assumption of proportional hazards, we included an interaction term between the log transformation of time in the study and NSAID use and no violation was found.

We adjusted for the following potential confounders: age (continuous), smoking status (never, past, current), alcohol consumption (rarely/never, 1–3 drinks/month, 1–6 drinks/week, ≥1 drinks/day), exercise (rarely/never, <1 times/week, 1–3 times/week, ≥4 times/week), history of high cholesterol (yes/no), cholesterol lowering medication use (yes/no), history of hypertension (yes/no), hypertension medication use (yes/no), body mass index (continuous), modified Charlson comorbidity score (continuous), indications of NSAID use score (continuous) and NSAID side effects or contraindications score (continuous). In addition we adjusted for randomized treatment assignment to aspirin and vitamin E. The modified Charlson comorbidity score and the scores for indications of NSAID use and NSAID side effects or contraindications were updated on a yearly basis. All other variables were assessed at baseline and not updated over time.

For the less than 100 women who were missing information on any of our confounders, we assigned these women to either the most frequent category or past user category for categorical variables and mean value for continuous variables.

Results

After excluding the sixteen women reported experiencing a prior stroke or TIA at baseline, we had 39,860 women eligible for this analysis whose baseline characteristics can be seen in Table 1. After a mean of 15.7 years of follow-up, 702 TIAs, 292 ischemic strokes with mRS 0-1, 233 ischemic strokes with mRS 2-3 and 98 ischemic strokes with mRS 4-6 occurred.

Compared to women who did not report using NSAIDs, women who reported using NSAIDs had multivariable-adjusted (95% CI) of 1.00 (0.77, 1.29) for TIA, 1.48 (1.04, 2.10) for functional outcome from stroke with mRS 0 to 1, 0.83 (0.52, 1.33) for mRS 2 to 3, and 1.33 (0.68, 2.59) for mRS 4 to 6 (Table 2).

Discussion

Results from this large cohort study suggest than NSAID use may be associated with an increased risk of stroke with mild functional outcome although it was not associated with an increase or decrease in the risk of TIA or more severe ischemic stroke outcomes.

NSAIDs are a heterogeneous class of drugs with different inhibitory effects on COX-1 and COX-2 (15, 16). While aspirin irreversibly binds to and inhibits COX-1, other NSAIDs bind reversibly to COX and only temporarily inhibit the enzymes. COX-1 activity affects the synthesis of thromboxane A_2 which causes platelet aggregation, vasoconstriction and smooth muscle proliferation. In contrast, COX-2 activity affects the production of prostacyclin which can cause inhibition of platelet aggregation, vasodilation and antiproliferation (17). By inhibiting prostacyclin formation, COX-2 may elevate blood pressure, accelerate atherogenesis and may predispose patients with a ruptured atherosclerotic plaque to a thrombotic event (18). It has also been suggested that the impact of COX-2 inhibitors on endothelial function and nitric oxide productions, blood pressure,

and volume retention and other renal effects may explain the increased risk of cardiovascular events among COX-2 users (1). The cardiovascular effects of nonselective NSAIDs may depend upon their balance of COX-1 and COX-2 inhibition. This may explain some of the variation in the risks of stroke amongst different NSAIDs (17). The balance of COX-1 and COX-2 may impact functional outcomes from stroke by influencing the amount of inhibition of platelet aggregation, vasodilation and antiproliferation that occurs in the vascular system.

Strengths of this study include the large number of participants and outcome events, prospectively collected data on NSAID use and potential confounders, and using medical record review to confirm self-reported strokes and TIAs. While there are limitations to using the mRS as our measure of functional outcome from stroke (19, 20), it is widely accepted for use in clinical trials (21–24) and can be assessed retrospectively from medical records allowing it to be determined for most, if not all, stroke events. It also accounts for prestroke disability (10), has strong test-retest reliability, interrater reliability and validity (19), and does not exhibit a “ceiling effect” often observed when using the Barthel Index (25). Since all women in the WHS had to be willing not to use NSAIDs during the trial, the participants in this study most likely had no indications or contraindications for NSAID use at baseline. Since most women were not using NSAIDs, we have a cohort similar to a new initiator cohort and may be able to determine the effect of initiating NSAID use.

Some important limitations should be noted. First, NSAID use was self-reported and the women did not specify the particular type of NSAID that they were using. Therefore, we are unable to determine if the associations between NSAID use and functional outcomes from stroke vary amongst specific NSAID types. Additionally, we may be diluting the effects of a particularly harmful NSAID but grouping it with a less harmful NSAID. Since the women were not supposed to use NSAIDs during the clinical trial, some women may have misreported their NSAID use. However, since data on NSAID use were collected prior to the stroke event, this misclassification is most likely non-differential. We also had to assume that NSAID use in the past month represented NSAID use for the following year similar to in other studies (26). Additionally, not all women answered the question on NSAID use. We did control for this in our analyses, but missing information could prevent us from observing the true effect of NSAID use on stroke, particularly if women who use NSAIDs are less likely to report their usage and more likely to experience a stroke than women who report not using NSAIDs. Finally, due to the limited number of moderate or severe strokes in our cohorts, we may have limited power to detect effects in these groups.

With respect to our outcomes, the smaller number of severe strokes may have limited our power for these analyses. We were unable to further stratify our ischemic stroke results by etiologic subtypes due to the small number of events for most subtypes. While we tried to control for confounding, the potential for residual and unmeasured confounding remains. Finally, since our cohort is composed primarily of white, middle-aged females, our results may not be generalizable to other populations.

Future studies will be needed in order to determine if our finding of an increased risk of stroke with mild functional outcomes among women who use non-aspirin NSAIDs can be replicated and to determine if specific NSAID formulations have different impact on the risk of functional outcomes from stroke.

Acknowledgments

Funding Sources

The WHS is supported by grants from the National Institutes of Health (CA047988, HL043851, HL080467, HL099355). Dr. Rist was funded by a training grant from the National Institute of Aging (AG-00158).

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Table 1

Baseline Characteristics of Women According to NSAID Use Status at Baseline in the Women's Health Study (n=39,860).*

Characteristic	
Mean (SD) age, y	54.6 (7.04)
Body mass index (SD), kg/m^2	26.1 (5.1)
History of hypertension, %	25.9
Antihypertensive medication use, %	13.8
History of high cholesterol, %	29.5
Cholesterol lowering medication use, %	3.1
Alcohol consumption, %	
Rarely/never	45.1
1–3 drinks/month	13.2
1–6 drinks/week	31.5
≥1 drinks per day	10.2
Randomized aspirin assignment, %	50.0
Randomized vitamin E assignment, %	50.0
Vigorous physical activity, %	
<200	68.6
200–599	13.0
600–1499	11.5
≥1500	6.8
Smoking status, %	
Never	51.0
Past	35.8
Current	13.1
Migraine, %	
Active migraine with aura	5.2
Active migraine without aura	7.8
Past history of migraine	5.4
Mean modified Charlson comorbidity score (SD)	0.2 (0.5)
Mean indications for NSAID use score (SD)	0.3 (0.5)
Mean NSAID side effect or contraindications score (SD)	0 (0.1)

Abbreviations: NSAID, non-steroidal anti-inflammatory drugs; std, standard deviation; kg/m^2, kilograms per meters-squared

*Numbers may not add up to 100% because of rounding or missing data.

Table 2

Multivariable-adjusted* Relative Risk of TIA and Functional Outcomes From Ischemic Stroke Using a Cox Model With Information on NSAID Use Updated Over Time (n=39,860).

	TIA (n=702)				mRS 0-1 (n=292)				mRS 2-3 (n=233)				mRS 4-6 (n=98)			
	n	**%**	**RR**	**(95 % CI)**	**n**	**%**	**RR**	**(95 % CI)**	**n**	**%**	**RR**	**(95% CI)**	**n**	**%**	**RR**	**(95 % CI)**
Non-user	615	87.6	1.00		238	81.5	1.00		203	87.1	1.00		84	85.7	1.00	
User	66	9.4	1.00	0.77, 1.29	38	13.0	1.48	1.04, 2.10	19	8.2	0.83	0.52, 1.33	10	10.2	1.33	0.68, 2.59
Missing	21	3.0	0.64	0.41, 0.99	16	5.5	1.27	0.76, 2.13	11	4.7	0.86	0.47, 1.58	4	4.1	0.80	0.29, 2.20

Abbreviations: TIA, transient ischemic attack; NSAID, non-steroidal anti-inflammatory drug; mRS, modified Rankin scale; RR, relative risk; CI, confidence interval

*Adjusted for age, smoking status, alcohol consumption, exercise, history of high cholesterol, cholesterol lowering medication use, history of hypertension, hypertension medication use, body mass index, modified Charlson comorbidity score, indications of NSAID use score, NSAID side effects or contraindications score and randomized treatment assignment to aspirin and vitamin E.