Nonsteroidal Antiinflammatory Drugs, Acetaminophen, and the Risk of Cardiovascular Events

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Background—Although randomized trials of cyclooxygenase-2 (COX-2) inhibitors have shown increased cardiovascular risk, studies of nonselective, nonsteroidal antiinflammatory drugs (NSAIDs) and acetaminophen have been inconsistent.

Methods and Results—We examined the influence of NSAIDs and acetaminophen on the risk of major cardiovascular events (nonfatal myocardial infarction, fatal coronary heart disease, nonfatal and fatal stroke) in a prospective cohort of 70 971 women, aged 44 to 69 years at baseline, free of known cardiovascular disease or cancer, who provided medication data biennially since 1990. During 12 years of follow-up, we confirmed 2041 major cardiovascular events. Women who reported occasional (1 to 21 d/mo) use of NSAIDs or acetaminophen did not experience a significant increase in the risk of cardiovascular events. However, after adjustment for cardiovascular risk factors, women who frequently (≥22 d/mo) used NSAIDs had a relative risk (RR) for a cardiovascular event of 1.44 (95% CI, 1.27 to 1.65) compared with nonusers, whereas those who frequently consumed acetaminophen had a RR of 1.35 (95% CI, 1.14 to 1.59). The elevated risk associated with frequent NSAID use was particularly evident among current smokers (RR=1.82; 95% CI, 1.38 to 2.42) and was absent among never smokers ($P_{interaction}$=0.02). Moreover, we observed significant dose-response relations: Compared with nonusers, the RRs for a cardiovascular event among women who used ≥15 tablets per week were 1.86 (95% CI, 1.27 to 2.73) for NSAIDs and 1.68 (95% CI, 1.10 to 2.58) for acetaminophen.

Conclusions—Use of NSAIDs or acetaminophen at high frequency or dose is associated with a significantly increased risk for major cardiovascular events, although more moderate use did not confer substantial risk. **(*Circulation*. 2006;113: 1578-1587.)**

Key Words: acetaminophen ■ aspirin ■ cardiovascular diseases ■ cyclooxygenase-2 inhibitors ■ nonsteroidal antiinflammatory drugs

Randomized intervention trials suggest that regular use of cyclooxygenase (COX) isoenzyme-2–selective inhibitors is associated with an elevated risk of serious cardiovascular events.[1–3] Traditional, nonaspirin, nonsteroidal antiinflammatory drugs (NSAIDs), such as ibuprofen or naproxen, inhibit COX enzymes less selectively. Whether these agents have a similar effect on cardiovascular risk remains unclear. Recently, investigators halted an Alzheimer disease prevention trial because of an excess of cardiovascular events in participants randomized to naproxen.[4] A study nested in the Norwegian Cancer Registry observed a nearly 3-fold greater risk of cardiovascular deaths among smokers who used ibuprofen.[5] Previous studies of NSAIDs and cardiovascular risk have been inconsistent: Some have observed an increased risk[6–13]; some have shown no effect[14–22]; others have suggested a potential cardioprotective benefit.[23–29] Fewer studies have investigated acetaminophen and cardiovascular events.[30] Nonetheless, acetaminophen and NSAIDs are associated with an increased risk of hypertension,[31–34] and the acetaminophen precursor phenacetin is associated with excess cardiovascular morbidity and mortality.[35]

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On the basis of present understanding of their mechanism of action and these prior studies, we hypothesized that frequent use of NSAIDs and acetaminophen, but not aspirin,

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may be associated with excess cardiovascular risk. Thus, we examined the influence of these analgesics on the risk of cardiovascular events in a large cohort of women enrolled in the Nurses' Health Study. Over a 12-year period, these participants provided detailed and updated information on their use. This prospective cohort study permitted a more comprehensive examination of the effect of these agents over a broader range of intake than would be immediately feasible in a placebo-controlled trial.

Methods

Participants

The Nurses' Health Study was established in 1976 when 121 701 US female registered nurses, aged 30 to 55 years, completed a mailed questionnaire. Follow-up questionnaires have been sent biennially thereafter to ascertain information on risk factors and identify newly diagnosed cardiovascular events and other health outcomes. A validated semiquantitative food-frequency questionnaire was added in 1980 to assess intake of nutrients.[36] In 1990, the questionnaire was expanded to include an assessment of patterns of NSAID and acetaminophen use. The institutional review board at the Brigham and Women's Hospital approved this study; all participants provided informed consent.

Assessment of Medication Use

As previously described,[37] beginning in 1990 we asked women if they regularly used aspirin, other antiinflammatory drugs "(eg, ibuprofen, Naprosyn [Roche Pharmaceuticals, Nutley, NJ], Advil [Wyeth, Madison, NJ])," and acetaminophen "(eg, Tylenol [McNeil Consumer & Specialty Pharmaceuticals, Fort Washington, Pa])," and the frequency of use. We updated these data biennially; beginning in 1998, for each agent, we also asked participants the number of tablets used per week. Early in the study, most women used standard-dose aspirin tablets; however, to reflect overall trends in consumption of low-dose aspirin, questionnaires after 1992 asked participants to convert intake of 4 "baby" aspirin to 1 adult tablet, and in 2000 we inquired specifically about baby or low-dose aspirin. COX-2 inhibitors were not introduced in the United States until 1999; hence, we first asked women in 2000 to report if they regularly used "Celebrex (Pfizer Inc, New York, NY) or Vioxx (Merck & Co Inc, West Trenton, NJ) (COX-2 inhibitors)" but did not inquire specifically about frequency or dose.

In a subsample of 200 women who reported aspirin use in 1990, we conducted a study to determine the reasons for use (91% response). The major reasons for use among women taking 1 to 6 and ≥7 aspirin tablets per week were headache (32% and 18%, respectively); arthritis and other musculoskeletal pain (30% and 50%); a combination of headache and musculoskeletal pain (16% and 15%); cardiovascular disease prevention (9% and 8%); and other reasons (13% and 9%).[38]

In 1999, we also sent a supplementary questionnaire to 4238 of the participants (91% response) to ascertain a 10-year detailed history of analgesic use.[39] Among aspirin users, 67% typically used 1 tablet per day, and 75% typically used tablets >300 mg. Among NSAID users, 73% used ibuprofen, 14% used naproxen, and 13% used other type; 53% typically used 2 tablets per day, 25% used 1 tablet per day, and 22% used ≥3 tablets per day. Among ibuprofen users, 62% reported using tablets between 100 and 299 mg. Among acetaminophen users, 55% typically used 2 tablets per day, 18% used 1 tablet per day, and 26% used ≥3 tablets per day; 69% used tablets of ≥500 mg. The major reasons for use among ibuprofen and acetaminophen users were muscle/joint pain (84% and 65%, respectively); headache (5% and 24%); backache (5% and 4%); and other reasons (6% and 8%).

Ascertainment of Cases

We requested written permission to acquire medical records from women who reported a myocardial infarction or stroke on our biennial questionnaire. We have previously described our methods for confirmation in detail.[38,40] Briefly, we confirmed myocardial infarction if the case met the World Health Organization criteria of symptoms and either typical ECG changes or elevated cardiac enzymes.[41] Infarctions of indeterminate age were excluded. We confirmed stroke according to criteria of the National Survey of Stroke. Myocardial infarctions or strokes that required hospital admission and for which confirmatory information was obtained by personal interview were designated as probable. We included all confirmed and probable cases because results were not substantially different after exclusion of probable cases (data not shown).

We identified deaths through the National Death Index and next of kin.[42] For all deaths attributable to coronary heart disease or stroke, we requested permission from next of kin to review medical records and death certificates. Fatal coronary heart disease was confirmed by records or autopsy or if coronary heart disease was listed as the cause of death on the death certificate and evidence of previous coronary heart disease was available. Fatal stroke was confirmed by medical records, death certificates, or telephone interview with next of kin.

Statistical Analysis

At baseline, we included all women who completed the long version of the 1990 questionnaire that included the medication questions. We excluded women who left the medication questions blank, reported a history of cancer (except nonmelanoma skin cancer), prior myocardial infarction, stroke, coronary artery bypass grafting/percutaneous coronary intervention, or angina. After these exclusions, 70 971 women were eligible for analysis. Person-time for each participant was calculated from the date of return of the 1990 questionnaire to the date of the first nonfatal myocardial infarction, nonfatal stroke, fatal coronary event, fatal stroke, death from any cause, or June 1, 2002, whichever came first. To minimize any potential bias related to either use or avoidance of analgesics related to symptomatic ischemic heart disease, we censored participants who reported coronary artery bypass grafting, percutaneous coronary intervention, or angina during follow-up; these events were not included as end points. In the main analyses, we used Cox proportional hazards modeling to control for multiple variables simultaneously and to compute 95% CIs and used the specific categories of frequency of use of acetaminophen, aspirin, and NSAIDs as detailed in the 1990 and 1992 questionnaires.[33] Some regrouping was required to adjust for different categories in later questionnaires. For each 2-year time period between assessments, we used the most updated information for each analgesic as well as other covariates. In secondary analyses, we also assessed the influence of the number of tablets per week, beginning follow-up with return of the 1998 questionnaire when these data were first collected. We also performed stratified analyses to examine potential interactions. We used SAS version 8.2 (Cary, NC). All probability values were 2 sided.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Among the 70 971 women, we documented 2041 cardiovascular events (814 nonfatal myocardial infarctions, 795 nonfatal strokes, 277 coronary heart disease deaths, and 155 fatal strokes) over 765 626 person-years. Compared with lower-frequency users, women reporting the highest levels of use of each analgesic were older, less likely to exercise regularly, more likely to be hypertensive, and had a higher body mass index and a greater number of cardiac risk factors (Table 1).

For both NSAIDs and acetaminophen, we observed no significant difference in risk of cardiovascular events across categories of use between 1 and 21 d/mo compared with nonusers (Table 2). However, compared with nonusers, women who used NSAIDs frequently (≥22 d/mo) had a significantly elevated risk for a cardiovascular event (age-

TABLE 1. Baseline Characteristics of the Study Cohort in 1990*

	Frequency of Use, d/mo				
	None	1–4	5–14	15–21	≥22
NSAIDs	n=44 843	n=12 989	n=5481	n=1705	n=5953
Mean age, y	57.2	53.9	54.3	55.5	57.8
Mean body mass index, kg/m^2†	24.7	25.0	25.5	26.0	26.7
Physical activity, mean MET/wk‡	16.0	16.0	15.3	14.0	14.4
Mean daily intake§					
Saturated fat, g	18.9	18.9	19.1	19.1	19.0
Folate, μg	425	428	435	441	460
Omega-3 fatty acids, mg	251	260	255	263	260
Alcohol, g	5.1	5.2	5.4	5.3	4.8
Hypertension, %	26.9	26.9	30.8	32.2	38.8
Diabetes mellitus, %	3.7	3.6	4.3	4.8	6.7
Hypercholesterolemia, %	35.0	36.3	38.0	39.9	42.5
Smoking history					
Past, %	37.1	40.5	41.4	41.2	42.2
Current, %	17.2	15.8	16.5	16.2	15.2
Postmenopausal, %‖	77.7	75.7	76.4	79.0	82.0
Past use of hormones, %	16.6	17.6	19.7	17.5	17.7
Current use of hormones, %	36.1	43.1	42.3	45.1	47.9
Parental myocardial infarction, age ≤60 y %	16.4	16.7	17.3	17.2	18.4
Current use					
Aspirin, %	49.2	43.5	41.7	33.2	24.4
Acetaminophen, %	41.4	49.0	46.5	41.8	41.4
Multivitamin, %	33.8	36.4	38.3	39.2	40.4
Cardiac risk factors, No.#					
0, %	37.0	36.7	33.2	29.6	26.2
1, %	37.2	37.1	36.0	37.3	34.7
2, %	19.2	19.4	22.5	24.7	25.9
≥3, %	6.6	6.9	8.3	8.5	13.2
Acetaminophen	n=40 438	n=19 827	n=6178	n=1809	n=2719
Mean age, y	57.1	54.9	55.3	56.4	57.8
Mean body mass index, kg/m^2†	24.8	25.0	25.3	25.6	26.0
Physical activity, mean MET/wk‡	16.3	15.2	14.7	14.8	13.8
Mean daily intake§					
Saturated fat, g	18.9	19.0	19.1	19.2	19.4
Folate, μg	429	425	438	436	458
Omega-3 fatty acids, mg	258	250	240	253	246
Alcohol, g	5.5	4.5	4.8	5.3	5.1
Hypertension, %	27.0	27.8	31.9	35.7	38.2
Diabetes mellitus, %	3.8	4.2	4.1	5.3	5.5
Hypercholesterolemia, %	34.9	37.0	39.1	39.8	40.6
Smoking history					
Past, %	38.2	38.9	39.5	42.7	39.0
Current, %	17.2	15.8	15.9	16.8	19.2
Postmenopausal‖	77.3	76.9	78.3	78.8	81.1
Past use of hormones, %	16.7	17.2	18.1	21.8	18.4
Current use of hormones, %	38.2	39.7	41.2	40.6	42.0
Parental myocardial infarction, age ≤60 y, %	16.6	16.5	17.2	17.7	17.3

TABLE 1. Continued

	Frequency of Use, d/mo				
	None	1–4	5–14	15–21	≥22
Current use¶					
Aspirin, %	52.5	35.6	35.9	30.4	29.4
NSAID, %	35.0	37.5	42.5	44.5	42.1
Multivitamin, %	34.3	35.0	38.4	38.3	43.2
Cardiac risk factors, No.#					
0, %	36.8	35.7	32.1	28.4	28.3
1, %	36.8	37.2	37.1	37.7	33.8
2, %	19.5	19.8	22.6	24.2	25.4
≥3, %	6.9	7.2	8.2	9.7	12.4
Aspirin	n=39 029	n=15 898	n=6395	n=2695	n=6954
Mean age, y	56.1	55.7	56.4	57.5	58.9
Mean body mass index, kg/m^2†	25.0	24.7	25.0	25.4	25.4
Physical activity, mean MET/wk‡	15.6	15.9	16.2	15.6	15.6
Mean daily intake§					
Saturated fat, g	18.9	19.0	19.1	19.0	18.9
Folate, μg	426	422	429	439	467
Omega-3 fatty acids, mg	256	247	249	257	262
Alcohol, g	4.8	5.3	5.5	6.2	5.7
Hypertension, %	27.6	25.6	28.7	33.0	36.2
Diabetes mellitus, %	4.3	3.2	3.3	4.2	5.0
Hypercholesterolemia, %	35.6	34.8	36.4	38.2	41.1
Smoking history					
Past, %	38.7	37.3	39.5	40.1	49.0
Current, %	17.1	15.9	15.2	16.9	19.0
Postmenopausal‖	77.3	76.6	77.6	78.7	81.1
Past use of hormones, %	17.5	15.9	17.4	17.9	17.3
Current use of hormones, %	38.0	39.7	40.4	40.1	41.5
Parental myocardial infarction, age ≤60 y, %	16.2	16.4	16.8	18.8	18.9
Current use¶					
Acetaminophen, %	50.8	37.3	32.9	29.0	26.4
NSAID, %	41.7	31.0	32.9	31.0	28.7
Multivitamin, %	33.2	34.9	38.0	39.7	43.8
Cardiac risk factors, No.#					
0, %	35.7	39.0	36.0	31.1	28.0
1, %	37.2	36.0	37.0	38.7	36.6
2, %	19.7	19.2	20.3	21.4	24.8
≥3, %	7.5	5.9	6.7	8.8	10.6

*Characteristics at baseline questionnaire in 1990. All values, other than age, have been age-standardized according to the age distribution of the cohort.

†The body mass index is the weight in kilograms divided by the square of the height in meters.

‡Metabolic equivalent tasks.

§Nutrient values represent the mean of energy-adjusted intake. Omega-3 fatty acids include n-3 eicosapentaenoic acid and n-3 docosahexaenoic acid.

‖Hormones are defined as postmenopausal estrogen or estrogen/progesterone preparations. Percentage of past and current use was calculated among postmenopausal women only.

¶Current use is defined as intake at least 1 day per month for analgesic categories.

#Cardiac risk factors are hypertension, hypercholesterolemia, diabetes mellitus, current smoking, body mass index ≥30.

adjusted relative risk [RR], 1.67; 95% CI, 1.46 to 1.89). This association was attenuated but remained significant after adjustment for cardiovascular risk factors and the other analgesic classes (multivariate RR, 1.44; 95% CI, 1.27 to 1.65). Moreover, we additionally adjusted for the effect of cardiovascular risk factors such as systolic and diastolic blood pressure and total cholesterol as continuous measures and observed similar associations (data not shown). We found a similar relationship for women using acetaminophen frequently (multivariate RR, 1.35; 95% CI, 1.14 to 1.59). In

TABLE 2. RR of Cardiovascular Events According to Frequency of Analgesic Use, 1990–2002*

	Frequency of Use, d/mo					
	None	1–4	5–14	15–21	≥22	*P* for Trend
NSAIDs						
Person-years	544 472	79 634	52 544	21 079	67 356	
No. of cases	1467	139	104	43	288	
Age-adjusted RR (95% CI)	1.0	0.96 (0.80–1.14)	1.01 (0.82–1.23)	0.98 (0.72–1.32)	1.67 (1.46–1.89)	<0.0001
Multivariate RR† (95% CI)	1.0	0.95 (0.80–1.14)	1.01 (0.82–1.24)	0.92 (0.68–1.25)	1.51 (1.33–1.73)	<0.0001
Multivariate RR‡ (95% CI)	1.0	0.95 (0.79–1.14)	1.00 (0.81–1.22)	0.91 (0.67–1.23)	1.44 (1.27–1.65)	<0.0001
Acetaminophen						
Person-years	546 800	108 179	54 166	20 596	35 344	
No. of cases	1441	221	143	68	168	
Age-adjusted RR (95% CI)	1.0	1.00 (0.87–1.17)	1.19 (1.00–1.42)	1.36 (1.07–1.74)	1.72 (1.47–2.03)	<0.0001
Multivariate RR† (95% CI)	1.0	0.99 (0.85–1.15)	1.12 (0.94–1.33)	1.25 (0.98–1.60)	1.41 (1.19–1.66)	<0.001
Multivariate RR‡ (95% CI)	1.0	0.98 (0.84–1.14)	1.09 (0.91–1.30)	1.22 (0.95–1.56)	1.35 (1.14–1.59)	0.0001
Aspirin						
Person-years	477 859	94 691	53 716	31 794	107 025	
No. of cases	1298	168	111	85	379	
Age-adjusted RR (95% CI)	1.0	0.72 (0.61–0.85)	0.77 (0.64–0.94)	0.92 (0.74–1.15)	1.11 (0.99–1.26)	0.11
Multivariate RR† (95% CI)	1.0	0.80 (0.68–0.94)	0.86 (0.70–1.05)	1.03 (0.82–1.29)	1.13 (1.00–1.27)	0.05
Multivariate RR‡ (95% CI)	1.0	0.80 (0.68–0.95)	0.85 (0.70–1.04)	1.00 (0.80–1.26)	1.07 (0.95–1.20)	0.25

*Cardiovascular events include nonfatal myocardial infarction, nonfatal stroke, fatal coronary heart disease, and fatal stroke. RRs are for women in each frequency category compared with women in the reference category of none.

†Multivariate RRs are adjusted for age, parental history of myocardial infarction before age 60 years (yes or no), history of diabetes mellitus (yes or no), history of hypercholesterolemia (yes or no), smoking history (never, past, current smoker), body mass index (<22, 22–24.9, 25–26.9, 27–29.9, ≥30), regular moderate or vigorous exercise (<1.7, 1.7–4.5, 4.6–10.5, 10.6–22.1, and >22.1 metabolic equivalent task score per week), postmenopausal hormone use (premenopausal, never, past, current), current multivitamin use (yes or no), energy-adjusted quintiles of folate (dietary and supplement), omega-3 fatty acids, saturated fat, alcohol (0, 0.1–4.9, 5.0–14.9, ≥15 g/d), and other analgesic categories.

‡Multivariate RRs are adjusted for aforementioned variables as well as history of hypertension (yes or no).

contrast with NSAIDs and acetaminophen, aspirin was not associated with an elevated risk of cardiovascular events, even in the highest-frequency category (multivariate RR, 1.07; 95% CI, 0.95 to 1.20); there was a modest inverse association with low-frequency aspirin use (multivariate RR, 0.80; 95% CI, 0.68 to 0.95 for 1 to 4 d/mo).

We considered the possibility that chronic inflammatory diseases associated with elevated cardiovascular risk as well as analgesic use may have influenced our results. However, controlling for such conditions did not materially alter our results. Compared with nonusers of each agent, the RR for frequent users of NSAIDs was 1.40 (95% CI, 1.22 to 1.60), and the RR for frequent users of acetaminophen was 1.33 (95% CI, 1.13 to 1.57), after adding history of gout, osteoarthritis, and rheumatoid arthritis to our multivariate model. Furthermore, the effect of NSAIDs and acetaminophen did not differ according to the presence or absence of these chronic conditions. Among women without gout, osteoarthritis, or rheumatoid arthritis, the multivariate RR was 1.66 (95% CI, 1.23 to 2.23) for frequent NSAID use and 1.30 (95% CI, 0.92 to 1.85) for frequent acetaminophen use. Among women with at least 1 of these conditions, the multivariate RR was 1.33 (95% CI, 1.14 to 1.56) for frequent NSAID use and 1.33 (95% CI, 1.10 to 1.62) for frequent acetaminophen use.

Previous data demonstrate that both NSAIDs and acetaminophen are independently associated with an elevated risk of hypertension.[32,33] Thus, we considered the possibility that the effect of these agents on cardiovascular risk may be mediated through this mechanism and adjustment for hypertension in our multivariate models may minimize a potential association. After adjusting for all cardiovascular risk factors except hypertension, we found that the multivariate RRs for women taking these agents frequently were, in fact, generally stronger (RR, 1.51; 95% CI, 1.33 to 1.73 for NSAIDs; RR, 1.41; 95% CI, 1.19 to 1.66 for acetaminophen; Table 2).

We also evaluated the influence of these agents on specific coronary heart disease end points (Table I in the online-only Data Supplement). For women who frequently used NSAIDs or acetaminophen, we observed a consistently elevated risk for nonfatal myocardial infarction, fatal coronary heart disease, and all coronary heart disease end points (multivariate RR, 1.58; 95% CI, 1.32 to 1.89 for NSAIDs; multivariate RR, 1.56; 95% CI, 1.26 to 1.93 for acetaminophen). However, aspirin was not associated with a significantly elevated risk of any coronary heart disease.

Similarly, women who reported NSAID use ≥22 d/mo experienced a significantly greater risk for stroke (multivariate RR, 1.29; 95% CI, 1.06 to 1.57; Table II in the online-only Data Supplement), although the risk associated with acetaminophen was somewhat attenuated. In contrast, frequent aspirin users did not experience any increased risk of stroke; moreover, low-frequency users had a significant

reduction in risk of stroke (multivariate RR, 0.72; 95% 0.56 to 0.93).

In 1998, participants reported the number of tablets per week as well as frequency. In secondary analyses, we examined the influence of tablets per week with follow-up beginning with return of the 1998 questionnaire (Table 3). For both NSAIDs and acetaminophen, the risk appeared to be related to increasing dose. Compared with participants who took no NSAIDs, the multivariate RR for women who used ≥15 tablets per week was 1.86 (95% CI, 1.27 to 2.73; *P* for trend≤0.001). Similarly, for acetaminophen, women who reported ≥15 tablets per week experienced a RR of 1.68 (95% CI, 1.10 to 2.58; *P* for trend=0.002). In contrast, neither increasing frequency of aspirin use nor increasing aspirin dose was associated with elevated risk of cardiovascular events.

Although the vast majority of NSAID users in the study used ibuprofen, we considered the possibility that other types of NSAIDs might have a differential influence on risk of cardiovascular events. Beginning in 1998, we first asked participants if they regularly used a NSAID other than ibuprofen at least 2 times a week. Among regular users of nonibuprofen NSAIDs, we observed a multivariate RR of 1.62 (95% CI, 1.21 to 2.15) compared with women who did not regularly use nonibuprofen NSAIDs.

The influence of NSAIDs and acetaminophen on cardiovascular disease was not significantly modified by participant age; aspirin use; body mass index; physical activity; or presence or absence of hypertension, hypercholesterolemia, or diabetes mellitus. The risk associated with frequent NSAID use appeared to be influenced by smoking status (*P* for interaction=0.02). Frequent use of NSAIDs was associated with a multivariate RR of 1.82 (95% CI, 1.38 to 2.42) among current smokers, 1.58 (95% CI, 1.28 to 1.95) among past smokers, and 1.11 (95% CI, 0.88 to 1.41) among nonsmokers. In contrast, smoking did not appear to influence the effect of acetaminophen on risk (*P* for interaction=0.97).

Because COX-2–selective inhibitors are associated with elevated cardiovascular risk, we also considered the possibility that differential use of these agents among frequent NSAID and acetaminophen users may have accounted for our findings. Thus, we conducted analyses in which we restricted follow-up through January 1, 1999, before COX-2–selective agents became available for widespread use. Our results remained essentially unchanged; the multivariate RR was 1.44 (95% CI, 1.25 to 1.65) for frequent NSAID use and 1.29 (95% CI, 1.08 to 1.54) for frequent acetaminophen use. In 2000, we first asked participants to report any use of COX-2–selective agents. In an analysis in which we excluded the 5202 participants who reported any use of COX-2–selective agents, we observed a multivariate RR of 1.45 (95% CI, 1.26 to 1.65) for frequent NSAID use and 1.35 (95% CI, 1.14 to 1.59) for frequent acetaminophen use. We evaluated the independent effect of COX-2 inhibitors with follow-up beginning with return of the 2000 questionnaire. Although we found an elevated risk of cardiovascular events among regular users of COX-2 inhibitors (age-adjusted RR, 1.72; 95% CI, 1.10 to 2.69), this was attenuated after multivariate adjustment (RR, 1.47; 95% CI, 0.93 to 2.33). Nonetheless, given the very limited follow-up and statistical power for the analysis of COX-2 inhibitor use, these results must be viewed as preliminary.

Discussion

In this large, prospective study, frequent (≥22 d/mo) use of either NSAIDs or acetaminophen was associated with a modest, although significant, elevated risk of cardiovascular events. This risk appeared to be dose related, with the greatest risk associated with use of ≥15 tablets per week.

Our results extend previous findings suggesting a relationship between use of NSAIDs and cardiovascular events. Three placebo-controlled trials have demonstrated an increased risk of serious cardiovascular events in participants randomized to COX-2 inhibitors.[1–3] An interim analysis of an Alzheimer disease prevention trial suggested similar risk with naproxen, although the full data have not been released.[4] Among users of various types of NSAIDs, a United Kingdom study observed a 20% to 30% elevated risk of myocardial infarction, and a Danish registry study found a 50% to 70% increased risk of hospitalization for myocardial infarction.[11,12] Ibuprofen has been associated with a nearly 2-fold higher risk of cardiovascular mortality in patients prescribed low-dose aspirin after hospitalization for cardiovascular disease.[7] A secondary analysis of the Physicians' Health Study showed a nearly 3-fold higher risk of myocardial infarction associated with NSAIDs in participants randomized to the aspirin arm.[8] NSAIDs have also been associated with an increased risk for congestive heart failure.[9,13] Finally, in a recent case-control study, recent use of any NSAID (including COX-2 inhibitors) and current use of naproxen were associated with a modestly elevated risk of serious coronary heart disease.[10]

Our findings might appear to contrast with prior studies that have observed either no relationship or an inverse association between NSAIDs and cardiovascular events. However, some of these studies were confined to patients with preexisting coronary heart disease,[17,23] rheumatoid arthritis,[26] or elderly individuals.[18] Other analyses were based largely on case-control studies that utilized prescription data, were not able to fully adjust for a range of cardiovascular risk factors, relied on participant recall after a cardiovascular event, assessed only a single measure of analgesic use, or did not differentiate high-frequency from occasional use.[15–18,20–27,29] In fact, our findings of a null relationship in the low- and moderate-frequency categories are consistent with such studies. Finally, although a meta-analysis concluded that certain NSAIDs, such as naproxen, may be associated with a potential cardioprotective benefit,[28] more recent studies, including data presented here, have not confirmed this finding.[10–12]

Our findings for NSAIDs are biologically plausible. NSAIDs inhibit antithrombotic prostacyclins to an extent similar to that of COX-2–selective inhibitors.[43] Although nonselective NSAIDs also inhibit COX-1, which synthesizes the prothrombotic thromboxane A_2, the relative balance between COX-1 and COX-2 activity is critical for vascular homeostasis. All NSAIDs may shift the equilibrium toward thrombosis and vasoconstriction.[44]

TABLE 3. RR of Cardiovascular Events According to Analgesic Frequency and Dose, 1998–2002*

	No. of Cases/Total No. of Person-Years	Age-Adjusted RR (95% CI)	Multivariate RR† (95% CI)
NSAIDs			
Days per week			
None	327/136 700	1.0	1.0
1	22/12 307	1.04 (0.67–1.60)	1.04 (0.67–1.62)
2–3	34/15 710	1.17 (0.82–1.67)	1.15 (0.80–1.66)
4–5	20/7239	1.48 (0.94–2.34)	1.33 (0.84–2.11)
≥6	71/18 767	1.68 (1.30–2.18)	1.51 (1.16–1.98)
P for trend		<0.0001	0.002
Tablets per week‡			
None	326/137 863	1.0	1.0
1–2	20/11 655	1.00 (0.64–1.58)	1.00 (0.63–1.59)
3–5	16/10 088	0.85 (0.51–1.41)	0.82 (0.49–1.37)
6–14	56/18 285	1.47 (1.10–1.95)	1.35 (1.00–1.81)
≥15	31/7550	2.09 (1.44–3.04)	1.86 (1.27–2.73)
P for trend		<0.0001	<0.001
Acetaminophen			
Days per week			
None	326/144 389	1.0	1.0
1	24/13 202	0.94 (0.62–1.42)	0.94 (0.62–1.44)
2–3	48/15 714	1.39 (1.02–1.89)	1.28 (0.94–1.75)
4–5	26/6689	1.66 (1.10–2.48)	1.49 (0.99–2.24)
≥6	50/10 728	1.77 (1.31–2.40)	1.50 (1.10–2.04)
P for trend		<0.0001	0.001
Tablets per week‡			
None	326/144 403	1.0	1.0
1–2	30/13 521	1.15 (0.79–1.67)	1.19 (0.81–1.76)
3–5	27/9692	1.23 (0.83–1.83)	1.16 (0.76–1.76)
6–14	45/12 873	1.55 (1.13–2.12)	1.47 (1.06–2.03)
≥15	25/4796	1.97 (1.29–3.00)	1.68 (1.10–2.58)
P for trend		<0.0001	0.002
Aspirin			
Days per week			
None	244/99 902	1.0	1.0
1	47/19 765	0.91 (0.66–1.25)	1.00 (0.73–1.39)
2–3	22/12 498	0.70 (0.45–1.09)	0.77 (0.50–1.20)
4–5	27/10 878	0.89 (0.59–1.33)	0.95 (0.63–1.43)
≥6	134/47 678	0.96 (0.78–1.19)	0.95 (0.76–1.18)
P for trend		0.20	0.57
Tablets per week‡			
None	250/106 020	1.0	1.0
1–2	57/29 116	0.71 (0.53–0.95)	0.78 (0.58–1.06)
3–5	57/23 484	0.91 (0.68–1.22)	0.96 (0.71–1.29)
6–14	81/23 743	1.15 (0.89–1.48)	1.09 (0.83–1.42)
≥15	10/3291	1.10 (0.58–2.10)	1.11 (0.58–2.11)
P for trend		0.18	0.41

*RRs are for women in each frequency category compared with women in the reference category of none.

†Adjustments as in multivariate model including hypertension, Table 2.

‡Twenty-five cases were missing data on NSAID tablets per week, 21 cases were missing data on acetaminophen tablets per week, 19 cases were missing data on aspirin tablets per week.

In our cohort, the increased risk of cardiovascular events associated with frequent NSAID use was markedly enhanced by cigarette smoking, which may potentiate platelet aggregation.[45] A case-control study of smokers in Norway observed a 2-fold higher risk of cardiovascular death among NSAID users and a nearly 3-fold higher risk among ibuprofen users.[5] Although we did not observe a significant interaction between NSAIDs and aspirin, our findings are consistent with a recent randomized trial of low-dose aspirin and risk of cardiovascular events in women.[46] That trial also failed to detect a significant interaction between concomitant NSAID use and the influence of aspirin; nonetheless, whereas aspirin was associated with a significantly reduced risk of cardiovascular events among nonsmokers, aspirin conferred a significant increase in risk (RR=1.30) among current smokers.[46]

Data examining the influence of acetaminophen on cardiovascular risk are comparatively sparse. A hospital-based case-control study observed a possible inverse association of long-term regular acetaminophen use with first myocardial infarction. However, the study was limited to men aged <55 years, and the observation was based on only 31 cases, was not statistically significant, and was attenuated after excluding subjects who reported angina symptoms.[30] The acetaminophen precursor phenacetin has been strongly associated with analgesic nephropathy as well as excess cardiovascular morbidity and mortality.[35] Furthermore, acetaminophen is associated with a dose-dependent risk of renal insufficiency,[47] an independent predictor of cardiovascular events.[48,49] Two previous prospective studies, including a study of participants in the present cohort, found an association between both acetaminophen and NSAIDs and incident hypertension.[32,33] In a recent analysis of women who provided more extensive data on analgesic usage, a significant, dose-dependent increase in risk of hypertension was observed among women using acetaminophen and NSAIDs irrespective of the reason for their use.[50] A randomized crossover study observed a significant rise in systolic blood pressure with short-term acetaminophen use.[31] Although only weakly inhibiting COX-1 and COX-2,[51] acetaminophen also inhibits prostaglandin production[52] and may impair endothelial function through depletion of glutathione.[53] Recent findings suggest that acetaminophen may mediate some of its effects through inhibition of a splice variant of COX-1, also known as COX-3.[51]

We observed a significant yet modestly protective benefit of aspirin use in the low-frequency categories (1 to 14 d/mo) on risk of stroke but not coronary heart disease. This dose range is consistent with present understanding about the minimum effective dose needed to fully inhibit thromboxane production.[54] Our findings are also consistent with the results of a recent randomized controlled trial of alternate-day, low-dose aspirin in healthy women that similarly demonstrated a significant reduction in stroke but not myocardial infarction.[46]

Our study had several strengths. First, we collected detailed information on analgesics from a large number of participants, permitting an investigation of use across a broader range of intake. Second, because we asked distinct questions about aspirin, NSAIDs, and acetaminophen, we were able to examine these drugs individually. Third, we obtained analgesic data prospectively, before diagnosis. Thus, any errors in recall would have tended to attenuate rather than exaggerate true associations, and any biases related to incomplete data collection from participants with fatal diagnoses were minimized. Fourth, to account for changes in participants' patterns of use over several years, we updated analgesic data biennially and used the most recent exposure and risk factor data for each 2-year time period. Finally, although studies that utilize prescription records have provided important data on the influence of prescription medications, our cohort of registered nurses likely provides more accurate data on actual consumption of over-the-counter medications, such as NSAIDs and acetaminophen. Furthermore, we collected more detail on cardiovascular risk factors, comorbid inflammatory conditions, and other potential confounders than typically available from large administrative databases.

Several limitations of our study deserve comment. Our study was observational, and analgesic use was self-selected. Thus, despite the strong biological plausibility of our results, it is possible that our findings could be related to the reason for which participants used NSAIDs or acetaminophen. However, high doses of these agents, including aspirin, were primarily used for analgesia,[38] and we did not find an increased risk of cardiovascular events among high-frequency aspirin users. Although we cannot completely exclude residual confounding by factors associated with frequent analgesic intake, our findings remained significant even after carefully controlling for known cardiovascular risk indicators as well as common reasons for chronic analgesic use, including gout, osteoarthritis, and rheumatoid arthritis. Additionally, when we stratified participants according to the presence or absence of these chronic conditions, our results remained largely unchanged. We also censored participants with angina or who underwent coronary revascularization, minimizing any potential protopathic bias related to analgesic intake for cardiovascular symptoms. Nevertheless, the strong evidence of increased cardiovascular risk among frequent NSAID or acetaminophen users, whether entirely attributable to the pharmacological consequences of the drugs, is of interest in itself.

The observational design of our study does not permit us to assign causality as would a randomized intervention trial designed to evaluate the effect of analgesics on cardiovascular risk. However, such a trial may not be feasible given the need for a large number of participants and prolonged follow-up, as well as ethical concerns given the findings from the COX-2 trials. As a result, some authorities have supported the use of an observational study such as ours to provide a timely and efficient assessment of drug safety.[55]

Our findings could have a substantial overall impact on public health. Concerns over the safety of COX-2–selective inhibitors will likely result in a decline in use of these agents in favor of traditional NSAIDs or acetaminophen. Ultimately, our results support the value of either long-term clinical trials or postmarketing surveillance of chronically used medications, including drugs that have been in long-standing clinical practice. Moreover, our findings support recommendations that long-term use of analgesics, including over-the-counter

drugs, should be undertaken in consultation with a physician.[56]

In summary, we did not observe a significantly elevated risk in cardiovascular events with less than daily use of NSAIDs and acetaminophen. However, use of NSAIDs or acetaminophen at high frequency or dose was associated with an increased risk, particularly among current smokers. Our results suggest the importance of carefully evaluating the ongoing use of analgesic agents and weighing their benefits with potential risks.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Concerns over the cardiovascular safety of cyclooxygenase-2 (COX-2)–selective inhibitors will likely result in a decline in use of these agents in favor of traditional, nonselective, nonsteroidal antiinflammatory drugs (NSAIDs) or acetaminophen. However, it remains unclear whether these analgesics may also be associated with cardiovascular risk. Thus, we examined the influence of NSAIDs and acetaminophen on the risk of major cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, fatal coronary heart disease, and fatal stroke) in a prospective cohort of 70 971 women, aged 44 to 69 years at baseline, with no prior history of cardiovascular disease or cancer, who provided data on medication use biennially since 1990. During 12 years of follow-up, we confirmed 2041 major cardiovascular events. Women who reported less than daily use of NSAIDs or acetaminophen (1 to 21 d/mo) did not experience a significant increase in the risk of cardiovascular events. However, after adjustment for a variety of cardiovascular risk factors, frequent ($\geq$22 d/mo) use of either NSAIDs or acetaminophen was associated with a modest, although significant, elevated risk of cardiovascular events, particularly among current smokers. This risk appeared to be dose related, with the greatest risk associated with use of $\geq$15 tablets per week. In contrast, frequent use of aspirin was not associated with excess cardiovascular risk. Our results support the importance of either long-term clinical trials or postmarketing surveillance of chronically used medications, including drugs that have been in long-standing clinical practice. Moreover, our findings support recommendations that long-term use of analgesics, including over-the-counter drugs, should be undertaken in consultation with a physician.