Secondary Data Analysis Exercise #2

Read the article by Ray, Stein, Daugherty and Griffin on NSAIDs and risk of serious coronary heart disease.

1. Why did Ray use person-years instead of persons?
2. Can you identify the design of the study?
3. What biases might have been introduced by using administrative data (as opposed to randomized trial data)?
4. What advantages does this administrative dataset have that an RCT might not?
5. How did the authors define "new users"?

When did NSAIDs go over the counter?

Non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease: an observational cohort study

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Summary

Background Non-aspirin, non-steroidal anti-inflammatory drugs (NANSAIDs) have complex effects that could either prevent or promote coronary heart disease. Comparison of the NANSAID rofexocib with naproxen showed a substantial difference in acute myocardial infarction risk, which has been interpreted as a protective effect of naproxen. We did an observational study to measure the effects of NANSAIDs, including naproxen, on risk of serious coronary heart disease.

Methods We used data from the Tennessee Medicaid programme obtained between Jan 1, 1987, and Dec 31, 1998, to identify a cohort of new NANSAID users (n=181 441) and an equal number of non-users, matched for age, sex, and date NANSAID use began. Both groups were 50–84 years of age, were not resident in a nursing home, and did not have life-threatening illness. The study endpoint was hospital admission for acute myocardial infarction or death from coronary heart disease.

Findings During 532 634 person-years of follow-up, 6362 cases of serious coronary heart disease occurred, or 11·9 per 1000 person-years. Multivariate-adjusted rate ratios for current and former use of NANSAIDs were 1·05 (95% CI 0·97–1·14) and 1·02 (0·97–1·08), respectively. Rate ratios for naproxen, ibuprofen, and other NANSAIDs were 0·95 (0·82–1·09), 1·15 (1·02–1·28), and 1·03 (0·92–1·16), respectively. There was no protection among long-term NANSAID users with uninterrupted use; the rate ratio among current users with more than 60 days of continuous use was 1·05 (0·91–1·21). When naproxen was directly compared with ibuprofen, the current-use rate ratio was 0·83 (0·69–0·98).

Interpretation Absence of a protective effect of naproxen or other NANSAIDs on risk of coronary heart disease suggests that these drugs should not be used for cardioprotection.

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Introduction

Non-aspirin, non-steroidal anti-inflammatory drugs (NANSAIDs)[1,2] could affect risk of acute myocardial infarction and other serious coronary heart disease. Findings of ex-vivo studies suggest that prediction of whether these effects are beneficial or harmful might be difficult because NANSAIDs have complex properties that could either prevent or promote coronary artery disease. Many NANSAIDs inhibit production of thromboxane and thus also inhibit platelet aggregation. Prevention of non-fatal myocardial infarctions by low-dose aspirin suggests that NANSAIDs could prevent coronary artery disease, an effect thought to be attributable to irreversible and almost complete inhibition of thromboxane produced by platelets.[3] Inflammation seems to have an important role in pathogenesis of atherosclerosis,[4,5] which suggests that NSAIDs in anti-inflammatory doses could reduce clinical manifestations of coronary artery disease.[6] Conversely, high doses of NSAIDs inhibit synthesis of prostacyclin, a potent endogenous platelet inhibitor,[7] which could raise risk of coronary heart disease, as could other dose-related effects of NSAIDs, such as hypertension.[8] However, up to now there have been few population-based studies of whether or not NANSAIDs affect risk of clinically important coronary heart disease in human beings.[9]

Results from a large trial of the new cyclooxygenase-2 (COX-2)-selective drug, rofecoxib,[10] have stimulated increased interest in this topic. That trial, which was designed to assess gastrointestinal safety of rofecoxib, compared patients randomly assigned to daily doses of either 50 mg rofecoxib or 1 g naproxen. The rofexocib and naproxen patients differed by occurrence of myocardial infarctions, 0·4% and 0·1%, respectively. Because there was no untreated group, we do not know whether this finding suggests a protective effect of naproxen or a harmful effect of rofexocib. Some data suggest that naproxen suppresses production of thromboxane and inhibits platelet aggregation by 88% for up to 8 h.[11] By contrast, because rofecoxib and other COX-2-selective drugs do not inhibit thromboxane synthesis,[10,11] they should not affect platelet aggregation by this mechanism. However, these drugs could increase risk of coronary heart disease because they inhibit prostacyclin formation.[7] In view of the widespread use of naproxen and other non-selective NANSAIDs, and the likelihood that such use will probably decline as that of COX-2-selective drugs rises, a differential effect of these two types of NANSAIDs on the risk of coronary heart disease has important public health ramifications.

We sought to quantify risk of myocardial infarction and fatal coronary heart disease among new users of generally prescribed NANSAIDs. We did the study before marketing of new COX-2-selective agents (celecoxib and rofecoxib) and thus did not include these drugs.

Methods

Study data

We obtained study data from Medicaid in Tennessee.[12] Medicaid computerised files allowed cohort identification, classification of cardiovascular risk factor status, and endpoint ascertainment. The files included: a central

registry of all individuals enrolled, linked with death certificates; records of prescriptions filled at the pharmacy; records of hospital admissions for people enrolled in Medicaid; records of visits to the emergency room, hospital outpatient department, outpatient surgical facility, and physician for those enrolled in Medicaid; and the nursing-home file.

Study participants

We compared new users of NANSAIDs between Jan 1, 1987, and Dec 31, 1998, with a demographically matched random sample of controls who had not used NANSAIDs. This design ensured that events early in drug use were recorded, which is important because NANSAIDs could have short-term and long-term effects on coronary heart disease. The design also allowed classification of patients' cardiovascular risk-factor status just before NANSAID use began, which avoids potential bias introduced by control for NANSAID-mediated modification of cardiovascular risk factors, such as hypertension.[8]

New use of a NANSAID was defined as prescription of a study drug, with no use of any NANSAID in the 365 days preceding the date this prescription was filled (t_0). This definition was further restricted to individuals who, at time t_0, had been enrolled for at least 365 days, were aged between 50 and 84 years, were not in a nursing home (t_0 and for the previous 365 days), and had no medical history suggesting non-cardiovascular life-threatening illness (cancer, HIV, renal failure, liver injury, respiratory failure, or other serious immunological disorders) at t_0 and for the previous 365 days. Follow-up of a new NANSAID user began at t_0 and continued until one of the following censorship times was reached: 365 days after last NANSAID use, end of the study (Dec 31, 1998), end of enrolment, death, age 85 years, entry into a nursing home, occurrence of non-cardiovascular life-threatening illness, or a study endpoint. To ensure that baseline characterisation of cardiovascular risk was not outdated, follow-up was stopped 5 years after t_0. For every new NANSAID user, we randomly selected an individual who was enrolled in Medicaid, who was not using a NANSAID at t_0 or in the past 365 days, as a control. The control was matched for sex and birth year, had to satisfy all membership criteria for NANSAID users, and furthermore, had to have at least one prescription for some other drug filled in the 365 days preceding t_0. Follow-up of controls began at t_0 and was calculated in a manner similar to that for new users, except that it would end if use of a NANSAID began subsequent to t_0.

Because the study took place over 11 years, and because use of NANSAIDs for a particular person would probably vary over this time, members of either cohort whose follow-up was stopped for any reason except death or a study endpoint could re-enter the cohort if, on that date, they met the criteria for entry. Thus, like most cohort studies, the same person could be a member of the new-user and control cohorts, but at different times, and could contribute only a single event to the analysis. To keep carryover effects to a minimum, cohort re-entry required at least 365 days without use of any NANSAID. At re-entry, baseline characteristics were updated to the new t_0. To measure the effect of cohort re-entry, we did an analysis restricted to the first period of follow-up of every person.

The study cohorts thus included 181 441 periods of new NANSAID use in 128 002 individuals and 181 441 matched control periods in 134 642 people. There were 69 314 individuals in both cohorts. In the primary analyses, these periods were the units of analysis.

Procedures

NANSAIDs and other drugs were identified from pharmacy records, which included date prescription was dispensed, drug, quantity, dose, and days of supply. For NANSAIDs, these data were checked to ensure that days of supply, from which we calculated prescription duration, were consistent with drug quantity. The most frequently used NANSAIDs were ibuprofen (38%) and naproxen (27%), for which individual analyses were done. Other NANSAIDs (grouped for analysis into a single category) were: non-acetylated salicylates (7%); fenoprofen (6%); indometacin (6%); piroxicam (3%); sulindac (3%); nabumetone (2%); meclofenamate (2%); diclofenac (1%); and phenylbutazone, tolmetin, diflunisal, ketoprofen, flurbiprofen, etodolac, ketorolac tometamol, oxaprozin, and bromfenac (all <1%). High-dose naproxen was defined as 1000 mg or greater, the dose at which platelet inhibition has been shown.[11] The cutoff points for ibuprofen (≥1800 mg) and other NANSAIDs were selected to provide comparable clinical doses.

During the study, COX-2-selective drugs were not available. Aspirin was used frequently in low doses, presumably as an antiplatelet agent, and thus was analysed separately as an indicator of cardiovascular disease.

The primary study endpoint was serious coronary heart disease, defined as acute myocardial infarction or death from coronary heart disease. Myocardial infarctions were defined as hospital admissions with a discharge diagnosis code (International Classification of Diseases, revision 9, clinical modification [ICD9-CM]) of 410.

We excluded the few inpatients who were discharged alive after a stay (including any transfers) of fewer than 3 days, because during the study, such short hospital visits were implausible for true myocardial infarctions. We also excluded patients who died from a cause other than ischaemic heart disease. Findings of validation studies of claims data[13,14] have shown that a main diagnosis code for acute myocardial infarction has a positive predictive value between 92%[13] and 95%,[14] and a sensitivity of 94%.[13]

Deaths from coronary heart disease, identified from death certificates, were defined as those with the underlying cause coded as ischaemic heart disease (ICD9 codes 410–414), not associated with hospital admission as defined above, and with no evidence of another cause (hospital admission at least 1 day before death with a main discharge diagnosis other than ischaemic heart disease). Although diagnostic coding for deaths from coronary artery disease is probably less accurate than that for myocardial infarction, inclusion is important, because coronary artery disease frequently manifests as sudden death outside of hospital. In one analysis, we broadened this definition to include out-of-hospital deaths from other vascular disease (ICD9 codes 390–459, 798, 799).

In one analysis we excluded cohort members with baseline heart failure, which was defined as one or more hospital admission or emergency-room visit for heart failure (diagnosis codes 428, 402.01, 402.11, 402.91, 404.01, 404.11, 404.13, 404.91, 404.93) in the 365 days preceding t_0, two or more outpatient visits, or concomitant prescriptions for loop diuretic and digitalis glycoside.

For periods of NANSAID use, every person-day of follow-up was classified as current (use on that day according to days of supply) or former (no use on that day) and by NANSAID dose. For both NANSAID and control periods, every day was also classified by use of prescribed aspirin, assuming that the cardioprotective effect persisted 7 days after last use.

To control for potential differences in baseline risk of coronary artery disease, we constructed an index of risk from medical history in the 365 days preceding t_0. This index included use of prescribed drugs to treat cardiovascular disease (anti-arrhythmics, angiotensin-converting-enzyme inhibitors, anticoagulants, anti-diabetics, aspirin, β-blockers, calcium-channel blockers, digitalis, lipid-lowering agents, loop diuretics, other antihypertensives, platelet inhibitors) and hospital admissions and emergency room visits for cardiovascular and other disease. Previous myocardial infarctions also were identified (diagnosis codes 410, 412, 429.7). Serious cardiovascular disease included stroke or other cerebrovascular disease (diagnosis codes 430–438), angina or coronary artery revascularisation (prescription for nitrate or other anti-anginal drug, diagnosis of angina [codes 411 or 413], or coronary artery revascularisation procedure), and peripheral arterial disease (diagnosis codes 440.2, 443.1, 443.9, 444.22, 444.81 or prescription of cilostazol, cyclandelate, or pentoxifylline). A summary risk score was created from regression models of effect of these factors on rates of study endpoints among controls, in which regression coefficients defined weights given to every factor. This score was used in all analyses, because results thus obtained were virtually identical to those from more complex models with detailed terms for cardiovascular disease medical history.

Statistical analysis

Estimates of rate ratios adjusted for potential differences between current NANSAID users were calculated from Poisson regression models. Covariates in the model, defined at t_0, included age, sex, race, residence in Standard Metropolitan Statistical Area, calendar year of t_0, time elapsed since t_0, reason for Medicaid enrolment (aged, disabled or blind, or uninsured, a group that became eligible under a special programme initiated in Tennessee in 1994),[15] coronary-artery-disease risk score, replacement oestrogen use (in women), non-cardiovascular hospital admissions, and absence of regular physician care (fewer than two visits). Tests for differences between individual NSAIDs were done with single degree-of-freedom contrasts with the Wald method to assess statistical significance.

All analyses were done with SAS version 8.0. All p values were two-sided. The study was approved by the Vanderbilt Committee for the Protection of Human Subjects. Informed consent of participants was not needed because the study met the US criteria for consent waiver: it posed minimum risk to, and could ultimately benefit the study population.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Table 1 shows characteristics of NANSAID and control cohorts. 70% of the cohort were women, and 67% were white. Duration of follow-up and demographic factors did not differ by much between NANSAID users and controls.

Both NANSAID users and controls had high baseline risk for cardiovascular disease (table 1). A fifth of the cohort had serious cardiovascular disease in the year before cohort entry, usually obstructive coronary artery disease or heart failure. Two-thirds had previously used one or more cardiovascular drugs, suggesting raised risk of cardiovascular disease; antihypertensives, hypoglycaemics, loop diuretics, and anti-anginals were the drugs that were usually used. Among women, just under a fifth used replacement oestrogens at baseline. About a third of the cohort had previous non-cardiovascular visits to hospital or emergency-department, and just over a quarter had fewer than two physician visits in the past year. There were no material differences for these factors between NANSAID users and controls.

	NANSAID users (n=181 441)	Controls (n=181 441)
Characteristic		
Mean time entered cohort	August 1993	August 1993
Follow-up (years, mean [SD])	1·5 (1·1)	1·4 (1·1)
Age (years, mean [SD])	63·8 (9·5)	63·8 (9·5)
Men	53 862 (30%)	53 878 (30%)
White	118 126 (65%)	123 656 (68%)
Standard Metropolitan Statistical Area	86 477 (48%)	84 306 (46%)
Medicaid enrolment		
Uninsured	39 624 (22%)	42 930 (24%)
Disabled	93 825 (52%)	91 439 (50%)
Aged	47 992 (26%)	47 072 (26%)
Serious cardiovascular disease in past year	39 943 (22%)	40 289 (22%)
Myocardial infarction	2899 (2%)	3112 (2%)
Stroke or other cerebrovascular disease	6347 (4%)	7354 (4%)
Angina or revascularisation	27 965 (15%)	27 520 (15%)
Heart failure	8591 (5%)	9484 (5%)
Peripheral vascular disease	6064 (3%)	5719 (3%)
Use of any cardiovascular drug in past year	121 882 (67%)	120 502 (66%)
Antiarrhythmic	4605 (3%)	4774 (3%)
Angiotensin-converting enzyme inhibitor	33 471 (18%)	32 490 (18%)
Anticoagulant	5040 (3%)	7551 (4%)
Aspirin	11 187 (6%)	10 638 (6%)
β-blocker	23 911 (13%)	23 939 (13%)
Calcium-channel blocker	42 569 (23%)	39 524 (22%)
Digitalis glycoside	17 149 (9%)	19 043 (11%)
Hypoglycaemic agent	31 922 (18%)	30 821 (17%)
Lipid-lowering drug	17 678 (10%)	16 472 (9%)
Loop diuretic	28 546 (16%)	26 916 (15%)
Nitrate	24 920 (14%)	22 705 (13%)
Other antihypertensive	41 096 (23%)	38 608 (21%)
Platelet inhibitor	6400 (4%)	6276 (3%)
Thiazide diuretic	47 882 (26%)	43 656 (24%)
Oestrogen use among women in past year	25 293 (20%)	22 355 (17%)
Non-cardiovascular inpatient or emergency room visit in past year	58646 (32%)	50935 (28%)
Fewer than two physician visits in past year	47719 (26%)	51651 (28%)

Data are numbers of individuals (%) unless otherwise stated.

Table 1: **Characteristics of the study cohorts**

Table 2 shows the rates of serious coronary heart disease in the two cohorts. There were 6362 cases of serious coronary heart disease in 532 634 person-years of follow-up, or 11·9 per 1000 person-years. Of these, 4224 (66%) were hospital admissions with a discharge diagnosis for acute myocardial infarction and 2138 (34%) were deaths coded as fatal coronary heart disease.

Within the current-use and former-use groups, rate of serious coronary heart disease did not differ by much from that of controls. When we compared current use of individual NANSAIDs with controls (table 3), we noted only minor differences between drugs. The rate ratio for naproxen was significantly lower than that for ibuprofen (p=0·03), but it was not significantly different from that for other NANSAIDs (p=0·35). The rate ratio for ibuprofen ≥1800 mg was significantly greater than that for lower doses. However, there were no significant dose-response trends for naproxen or other NANSAIDs.

	Person-years	Coronary heart disease	Rate per 1000 person-years	Adjusted rate ratio* (95% CI)
NANSAID users	275 565	3313	12·02	1·03 (0·98–1·08)
Current use	65 502	841	12·84	1·05 (0·97–1·14)
Former use	210 063	2472	11·77	1·02 (0·97–1·08)
Control cohort	257 069	3049	11·86	1·00

*Adjusted with Poisson regression.

Table 2: **Rates of serious coronary heart disease by study cohort and NANSAID use**

To identify subgroups most likely to benefit from NANSAID anti-inflammatory and antiplatelet effects, we classified use of NANSAIDs by duration and dose (table 4). The rate ratio for long duration of use (>60 days) was identical to that for use of shorter duration. Among long-duration users, the rate ratios for high doses did not differ by much from those for low doses. The rate ratio for high-dose naproxen use did not differ from those for ibuprofen or other individual NANSAIDs ($p \geq 0{\cdot}25$).

To test the robustness of study definitions, we did several alternative analyses that altered both composition of the cohort and endpoint definition (table 5). In these analyses we also directly compared current use of naproxen with that for ibuprofen. To assess the extent to which unmeasured low-dose aspirin use might affect findings, we limited the cohort by exclusion of those with baseline history of myocardial infarction or stroke (for whom aspirin was most likely to be prescribed). All rate ratios did not differ by much from those for the original cohort (table 5).

Some data suggest NANSAIDs could worsen heart failure,[16] and thus increase risk of serious coronary heart disease, thus we did an analysis that excluded cohort members with baseline heart failure; findings did not differ from those of the original cohort. Results of several aspirin studies show a different pattern of findings for fatal and non-fatal myocardial infarctions,[17] thus we did an analysis that excluded deaths from coronary heart disease (table 5). There was a small increase in the rate ratio for all NANSAIDs but none of the rate ratios for naproxen differed significantly from 1 (reference). Classification of deaths from coronary heart disease could be affected by the few data available at time of death, thus we did an analysis that included 1746 deaths coded as attributable to vascular disease other than ischaemic heart disease (table 5); results differed little from those of the primary analysis.

We also did several alternative analyses that tested the appropriateness of the statistical methods. To assess the effects of allowing individuals to appear in the cohort more than once, we restricted the cohort to the first period of follow-up. Rate ratios for use of current naproxen, ibuprofen, and other NANSAIDs were, respectively, 0·97 (0·79–1·20), 1·17 (1·00–1·38), and 1·05 (0·89–1·23). To assess the effect of possible changes in baseline covariates, we did an analysis restricted to 1 year of follow-up; the respective rate ratios were 1·01 (0·83–1·23), 1·19 (1·02–1·40), and 1·17 (1·00–1·38). To assess the possibility of an excess of events early in NANSAID therapy, we restricted follow-up to 60 days; the respective rate ratios were 1·09 (0·80–1·49), 1·36 (1·06–1·75), and 1·35 (1·05–1·75). To assess the requirement that controls have a prescription filled before baseline, we excluded 4% of new NANSAID users who did not meet this criterion, with resulting rate ratios of 0·95 (0·82–1·10), 1·12 (0·99–1·25), and 1·02 (0·90–1·15). Finally, to ascertain whether recent discontinuation of NANSAIDs was linked to events, we assessed people in the first 30 days after cessation of the drug. The rate ratio for this category compared with controls was 0·97 (0·89–1·07).

Discussion

Although effects of aspirin on coronary artery disease have been studied extensively,[3] there has been little investigation of widely used NANSAIDs. Our data suggest that, in a high-risk population of people 50 years of age or older, non-selective NANSAIDs neither increase nor decrease risk of serious coronary heart disease. Our rate ratio estimate for serious coronary heart disease is consistent with data from a case-control study of myocardial infarctions nested in a cohort of 164 769 women,[9] in which the investigators reported an odds ratio of 1·32 (0·97–1·81) for current NANSAID use.

The unexpected finding from the rofecoxib trial of a four-fold difference between this drug and naproxen in rates of myocardial infarction was interpreted as a protective effect of naproxen.[10] This hypothesis has now been discussed in both scientific[18] and lay circles,[19] in ways that might encourage the interpretation that naproxen is

	Person-years	Coronary heart disease	Rate per 1000 person-years	Adjusted rate ratio* (95% CI)
Other or multiple NANSAID	23 196	301	12·98	1·03 (0·92–1·16)
High dose	15 424	205	13·29	1·07 (0·93–1·24)
Low dose	7771	96	12·35	0·94 (0·77–1·16)
Naproxen	17 692	201	11·36	0·95 (0·82–1·09)
≥1000 mg	12 327	144	11·68	1·00 (0·84–1·18)
<1000 mg	5365	57	10·62	0·83 (0·64–1·09)
Ibuprofen	24 614	339	13·77	1·15 (1·02–1·28)
≥1800 mg	15 751	231	14·67	1·27 (1·11–1·45)
<1800 mg	8864	108	12·18	0·95 (0·78–1·15)
NANSAID use				
Former	210 063	2472	11·77	1·02 (0·97–1·08)
Control	257 069	3049	11·86	1·00

*Adjusted with Poisson regression.

Table 3: **Rates of serious coronary heart disease by specific NANSAID**

	Person-years	Coronary heart disease	Rate per 1000 person-years	Adjusted rate ratio (95% CI)†
Duration >60 days	15 354	213	13·87	1·05 (0·91–1·21)
Other NANSAID				
High dose	3877	42	10·83	0·84 (0·62–1·14)
Low dose	1969	25	12·70	0·92 (0·62–1·36)
Naproxen				
≥1000 mg	3174	44	13·86	1·07 (0·80–1·45)
<1000 mg	1375	22	16·00	1·13 (0·74–1·72)
Ibuprofen				
≥1800 mg	2994	50	16·70	1·33 (1·01–1·77)
<1800 mg	1964	30	15·27	1·09 (0·76–1·57)
Duration ≤60 days	50 149	628	12·52	1·05 (0·96–1·15)
Former	210 063	2472	11·77	1·02 (97–1·08)
Control	257 069	3049	11·86	1·00

*Number of previous days of current NSAID use with gaps of less than 7 days allowed. †Adjusted with Poisson regression.

Table 4: **Rates of serious coronary heart disease by duration of continuous NANSAID use***

	Number of events	Rate ratio (95% CI)		
		All NANSAID current use	Naproxen *vs* control	Naproxen *vs* ibuprofen
Original cohort	6362	1·05 (0·97–1·14)	0·95 (0·82–1·09)	0·83 (0·69–0·98)
Excluding cohort members with previous myocardial infarction or stroke	5595	1·05 (0·97–1·14)	0·94 (0·80–1·09)	0·83 (0·69–1·01)
Excluding cohort members with baseline heart failure	5564	1·08 (1·00–1·18)	0·99 (0·85–1·15)	0·85 (0·71–1·02)
Excluding deaths from coronary heart disease	4224	1·22 (1·11–1·33)	1·10 (0·94–1·30)	0·87 (0·71–1·06)
Including other vascular deaths	8102	0·98 (0·92–1·05)	0·91 (0·80–1·03)	0·86 (0·74–1·01)

*All rate ratios adjusted with Poisson regression.

Table 5: **Alternative analyses***

cardioprotective.[18,19] We thus did several analyses to test the hypothesis that naproxen has a unique protective effect of a size sufficient to explain the findings of the rofecoxib trial.

We did not find consistent evidence for this hypothesis. The overall rate ratio for naproxen was not significantly different from 1 (reference). We also did not find evidence that naproxen was protective for patients in whom the benefits of an anti-platelet effect were most likely to be present: those with doses of at least 1000 mg (thought to produce substantial and sustained antiplatelet effects)[11] and with more than 60 days of uninterrupted use. In this group, the rate ratio for naproxen did not differ from that for NANSAID non-users or from the ratios for comparable users of either ibuprofen or other NANSAIDs. We also directly compared naproxen with ibuprofen. These two groups will probably be closely similar with respect to unmeasured potential confounders that might differ between NANSAID users and non-users. In our analysis, the rate ratio for naproxen was slightly lower than that for all NANSAIDs. Even if this difference is attributable to a protective effect of naproxen, the size is insufficient to explain the findings of the rofecoxib trial.

The absence of a large protective effect for naproxen in our study could be explained in part by differences in the populations studied. Most NANSAID use in the community is for acute pain and symptoms of osteoarthritis,[1,2] whereas patients in the rofecoxib study had rheumatoid arthritis diagnosed, which might affect both risk of coronary artery disease[20,21] and effects of NSAIDs. The rofecoxib protocol prohibited aspirin use, and thus such use would probably have been lower than that in our study. However, the Medicaid cohort had an approximately four-fold higher incidence of serious coronary heart disease than did the patients in the rofecoxib trial,[10] which is evidence against the hypothesis that naproxen might differentially benefit high-risk patients.

Our study had several limitations. We used a computerised database of medical histories to define exposure to NANSAIDs and to identify serious coronary heart disease. Automated pharmacy records have been found to be an excellent unbiased source of information on drug use.[22–25] Although some NANSAIDs could be obtained over the counter during the study, Medicaid paid for these NANSAIDs when prescribed, and thus patients had strong economic incentive to obtain these drugs by prescription. In studies of Medicaid patients from Tennessee admitted to hospital for peptic ulcer,[1] colon cancer,[26] and renal failure,[27] among people who had no active prescriptions for NANSAIDs at admission, only 4% had such use noted in their chart. Conversely, in a phone-interview survey with medication container review, among people with active NANSAID prescriptions,[28] more than 90% reported current use of these drugs. However, some exposure misclassification is inevitable and would probably bias towards the null.

Were the findings for NANSAID users affected by confounding from risk factors for coronary heart disease? Several lines of evidence suggest this possibility was not the case. The Medicaid database provides extensive information on medically treated risk factors such as hypertension, diabetes, angina, and previous episodes of serious cardiovascular disease. At baseline, individuals starting use of NANSAIDs and controls had virtually identical prevalence of these risk factors, suggesting absence of systematic differences in risk of cardiovascular disease between these cohorts. Furthermore, the rate ratio estimates presented were calculated from models that controlled for these factors.

Because the study database did not have information on smoking, obesity, inactivity, and diet, these lifestyle factors could be confounders. However, in other studies in this population, smoking—potentially the strongest such confounder—has not varied with NANSAID use.[1,29] Furthermore, the effect of these lifestyle factors is shown by raised prevalence of medical risk factors such as hypertension or angina; these are controlled for in our analysis. Although residual confounding by behavioural or lifestyle factors is possible, the fact that risk for former non-current users of NANSAIDs was virtually identical to that of non-users suggests that the size of such confounding is not large.

Although our study had information on prescribed aspirin use, rates of use were low, and many patients were probably using over-the-counter aspirin. This factor would introduce bias only if aspirin use differed in accordance with NANSAID status. In studies of peptic ulcer,[1,29] colon cancer,[26] and renal failure,[27] this difference did not occur. In our cohort, exclusion of members with previous myocardial infarction or stroke—the group most likely to receive aspirin—did not significantly change findings.

Absence of a protective effect of naproxen or other non-selective NANSAIDs suggests that none of these drugs should be used for cardioprotection in the absence of evidence from randomised controlled trials to lend support to such a practice.

Contributors

W A Ray wrote the initial drafts of the study protocol and the report, and did the statistical analyses. M R Griffin and C M Stein contributed to the initial design of the study and helped revise both the protocol and the report. J R Daugherty and K Hall contributed to the study protocol and did computer programming.

Conflict of interest statement

M R Griffin is a consultant for Merck Research Laboratories and W A Ray has consulted for Merck in the past year, but none of the funding for this study was provided by any pharmaceutical company.

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