Published in final edited form as:

Am J Med. 2011 July ; 124(7): 614–620. doi:10.1016/j.amjmed.2011.02.025.

Harmful Effects of NSAIDs among Patients with Hypertension and Coronary Artery Disease

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Abstract

BACKGROUND—There is limited information about the safety of chronic nonsteroidal anti-inflammatory drugs (NSAIDs) in hypertensive patients with coronary artery disease.

METHODS—This was a post hoc analysis from the International Verapamil Trandolapril Study (INVEST), which enrolled patients with hypertension and coronary artery disease. At each visit, patients were asked by the local site investigator if they were currently taking NSAIDs. Patients who reported NSAID use at every visit were defined as chronic NSAID users, while all others (occasional or never users) were defined as nonchronic NSAID users. The primary composite outcome was all-cause death, nonfatal myocardial infarction, or nonfatal stroke. Cox regression was used to construct a multivariate analysis for the primary outcome.

RESULTS—There were 882 chronic NSAID users and 21,694 nonchronic NSAID users ($n = 14,408$ for never users and $n = 7286$ for intermittent users). At a mean follow-up of 2.7 years, the primary outcome occurred at a rate of 4.4 events per 100 patient-years in the chronic NSAID group, versus 3.7 events per 100 patient-years in the nonchronic NSAID group (adjusted hazard ratio [HR] 1.47; 95% confidence interval [CI], 1.19–1.82; $P = .0003$). This was due to an increase in cardiovascular mortality (adjusted HR 2.26; 95% CI, 1.70–3.01; $P = .0001$).

CONCLUSION—Among hypertensive patients with coronary artery disease, chronic self-reported use of NSAIDs was associated with an increased risk of adverse events during long-term follow-up.

Keywords

Coronary artery disease; Hypertension; Myocardial infarction; Nonsteroidal anti-inflammatory drugs; NSAIDs

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Conflict of Interest: Drs. Bavry, Khaliq, and Gong have no financial disclosures.

Authorship: This work is original, and all authors significantly contributed to this paper and accept responsibility for its scientific content.

Clinical trials and systematic reviews have shown that selective cyclooxygenase-2 inhibitors increase the hazard for myocardial infarction.^{1–6} This finding likely resulted in more frequent use of nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) as an alternative for chronic pain syndromes; however, current data are incomplete in regard to the cardiovascular safety profile of these agents.^{7,8}

Among patients with a low prevalence of coronary artery disease and aspirin use, studies have consistently documented increased cardiovascular risk with diclofenac.^{9–11} Naproxen and ibuprofen are generally regarded as safer agents;¹² however, a network meta-analysis in over 100,000 patients documented the highest risk for stroke with ibuprofen.¹³ Also, a randomized trial designed to prevent Alzheimer's dementia with the use of NSAIDs was terminated early due to a possible excess in cardiovascular events with naproxen.¹⁴

In patients with established coronary artery disease, aspirin is unequivocally beneficial;¹⁵ however, data about concomitant use of aspirin and NSAIDs are limited. In one study, the use of aspirin plus ibuprofen (at least 1200 mg daily) after an acute myocardial infarction was associated with a 2.2-fold increase in mortality, despite a relatively short duration of use (median 37 days).¹⁶ A brief report in post-myocardial infarction patients also documented increased mortality with aspirin plus ibuprofen;¹⁷ however, another report found no effect on mortality.¹⁸

In summary, the current database is incomplete regarding the long-term safety of NSAIDs, especially among patients with coronary artery disease. Additionally, most of these studies were not designed to capture or control blood pressure during follow-up, and furthermore, they lacked appropriate prospective cardiovascular outcome data capture and adjudication. The International Verapamil Trandolapril Study (INVEST) provided an opportunity to further investigate the association between chronic NSAID use, on-treatment blood pressure, and adverse outcomes. Therefore, the aim of this study was to explore the association between chronic NSAID use, blood pressure, and adverse cardiovascular outcomes among hypertensive patients with coronary artery disease within the INVEST.

METHODS

Original Study Protocol

INVEST was an international randomized trial conducted in 14 countries that compared the effects of a calcium antagonist (verapamil SR)-based strategy with a beta-blocker (atenolol)-based strategy for hypertension among patients with stable coronary artery disease. Enrollment was from September 1997 to February 2003. The study was conducted according to the principles of the Declaration of Helsinki. Local ethics committees approved the protocol, and written informed consent was obtained from all subjects. The main outcomes have been previously reported.¹⁹ Patients at least 50 years of age with hypertension and clinically stable coronary artery disease were eligible for enrollment. Protocol-scheduled follow-up visits occurred every 6 weeks for the first 6 months and then biannually until 2 years after the last patient was enrolled.

Post Hoc Analysis/Outcomes

At baseline and every follow-up visit, patients were asked if they were currently taking aspirin (yes or no) and NSAID medications (yes or no). These data were recorded by the local site physician investigator. We categorized NSAID exposure into chronic use (defined as individuals who reported NSAID use at baseline and each follow-up visit) versus nonchronic use (defined as individuals who never took NSAIDs or reported use at only some visits).

The primary outcome was the first occurrence of all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke. Secondary individual outcomes were all-cause mortality, cardiovascular mortality, total myocardial infarction (nonfatal plus fatal myocardial infarctions), and total stroke (nonfatal plus fatal strokes). Outcomes were adjudicated by a blinded events committee by review of pertinent patient records, hospital records, and death registries.

To further assess the long-term cumulative effect of chronic NSAIDs on all-cause mortality, we searched the national death index among United States (US) patients up to 5 years after INVEST follow-up was concluded. To be considered a confirmed death, 4 of 5 matches of the following were required: name, social security number, date of birth, city, and state. Patients who did not experience any component of the primary outcome were censored at the last study visit. For the extended follow-up analysis, patients who did not appear in the national death index were censored on the day the death index search was completed.

Statistical Analysis

Baseline characteristics were reported as frequencies. Continuous and categorical variables were compared with Student's *t* test and the chi-squared test, respectively. Kaplan-Meier analysis was used to plot the time to first occurrence of the primary outcome, and the 2 groups were compared with the log-rank test. A Cox proportional hazards model was used to compare chronic and nonchronic NSAID users for risk of the primary and secondary outcomes using stepwise selection of baseline covariates. The percentage of visits with aspirin use also was considered as a covariate. A *P* value of .2 was used to select covariates to enter the model, while a *P* value of .05 was used to retain covariates in the model. For each treatment group, the hazard ratios (HR) for the primary outcome were displayed for on-treatment systolic blood pressure in 10 mm Hg increments, using 130 to <140 mm Hg as the referent.

To adjust for the independent contribution of baseline characteristics on the risk of an adverse outcome, chronic NSAID users were compared with a propensity-matched sample (1:1 ratio) of nonchronic NSAID users. A propensity score was calculated using the SAS PROC logistic procedure by determining the probability for each patient to be in one group or another. Then for each chronic NSAID user, a nonchronic NSAID user with approximately the same propensity score (± 0.01) was randomly selected. The 2 propensity-matched groups were then compared using the same Cox regression analysis as described above.

All outcomes were reported from Cox regression analysis unless specifically noted otherwise and were expressed as HR and 95% confidence intervals (CI). Analyses were performed with SAS software version 9.2 (SAS Institute, Inc., Cary, NC).

RESULTS

There were 882 chronic NSAID users and 21,694 nonchronic NSAID users ($n = 14,408$ for never users and $n = 7286$ for intermittent users). There were significant differences between the chronic and nonchronic groups at baseline. For chronic NSAID versus nonchronic NSAID users, the mean age was 65.3 years versus 66.1 years ($P = .02$), women were 66.9% versus 51.5% ($P < .0001$), diabetics were 33.1% versus 28.2% ($P = .0014$), and a history of peripheral arterial disease was present in 26.5% versus 11.4% ($P < .001$), respectively. Chronic NSAID users also were less likely to use aspirin and lipid-lowering medications. Detailed baseline characteristics and nonstudy medications are summarized in Table 1.

Mean duration of follow-up for the total patient cohort was 2.7 years (median 2.7 years, 60,970 patient-years), and the mean number of follow-up visits per patient was 8.7 (SD 3.9). Gastrointestinal bleeding occurred in 0% of the chronic NSAID group versus 0.8% of the nonchronic NSAID group. Mean systolic and diastolic blood pressures were slightly but statistically lower in the chronic NSAID group throughout follow-up (Figure 1).

Figure 2 shows the Kaplan-Meier curve for time to the primary outcome by NSAID group. The primary outcome occurred at a rate of 4.4 events per 100 patient-years for chronic NSAID users versus 3.7 events per 100 patient-years for nonchronic NSAID users (adjusted HR 1.47; 95% CI, 1.19–1.82; $P = .0003$). Independent predictors for the primary outcome are displayed in Table 2. Compared with never users, chronic NSAID users were associated with harm (adjusted HR 1.29; 95% CI, 1.05–1.60; $P = .018$), while intermittent users were not (adjusted HR 0.73; 95% CI, 0.66–0.80; $P < .0001$). In the analysis of chronic NSAID users propensity-matched to nonchronic NSAID users, the adjusted HR for the primary outcome was 1.60 (95% CI, 1.18–2.17; $P = .0023$). Incidence and event rates for additional outcomes are summarized in Table 3.

Blood pressure modified the relationship between chronic NSAID exposure and adverse outcomes (P for interaction $< .0001$). The adjusted HR for the primary outcome and mean systolic blood pressure (in increments of 10 mm Hg) was displayed for the 2 groups in Figure 3. For chronic NSAID users, the risk of the primary outcome was markedly increased for mean systolic blood pressure > 150 mm Hg (although with wide confidence intervals) compared with patients with a mean systolic blood pressure of 130–140 mm Hg.

As an added note, during the extended follow-up of the US cohort, there were 833 chronic NSAID users and 16,298 nonchronic NSAID users. Over a mean duration of follow-up of 7.6 years (median 8.4 years, 130,772 patient-years), all-cause mortality was significantly increased from earlier self-reported chronic NSAID use (adjusted HR = 1.24; 95% CI, 1.05–1.47; $P = .013$).

DISCUSSION

Among hypertensive patients with coronary artery disease, chronic self-reported NSAID use over a mean of 2.7 years was associated with a 47% increase in the first occurrence of death, nonfatal myocardial infarction, or nonfatal stroke. This was due to a 90% increase in all-cause mortality (which persisted into extended follow-up of more than 5 years), a 126% increase in cardiovascular mortality, and a 66% increase in total myocardial infarctions. There was no significant difference in total stroke.

Because we did not have information on NSAID type or dose, our findings should be considered a class effect. It is unknown if a particular agent was responsible for the excess risk. The ongoing Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION) trial should help to determine the relative safety of these 3 particular NSAIDs.²⁰ Placebo-controlled trials also are needed to determine the overall safety of NSAIDs. Until randomized trial data are reported, clinical judgment should be exercised in caring for at-risk individuals.

It is noteworthy that the average age of our study participants was 65 years and approximately one third were older than 70 years. Study participants also had clinically stable coronary artery disease, including remote myocardial infarction in one third. Approximately 50% of participants were chronically taking aspirin throughout the study. A recent American Geriatrics Society Panel on the treatment of chronic pain in the elderly recommended acetaminophen as the first-line agent.²¹ The panel suggested that nonselective NSAIDs or cyclooxygenase-2-specific agents only be used with extreme caution. Our findings support this recommendation.

Chronic NSAID users had a lower mean systolic blood pressure at baseline and throughout the follow-up period. The current opinion is that NSAIDs increase blood pressure, but this has not been established with long-term use from studies that focus on blood pressure and blood pressure control. In one meta-analysis, short-term use of NSAIDs was associated with a 5 mm Hg increase in systolic blood pressure;²² however, a more recent meta-analysis of short-term use of NSAIDs documented a significant blood pressure-raising effect only for ibuprofen.²³ Despite lower mean systolic blood pressure and other characteristics that would have been expected to decrease the risk for adverse events (for example, younger age and less frequent history of myocardial infarction and congestive heart failure), the net effect from multivariate modeling and propensity matching was an increase in long-term adverse cardiovascular events.

The Physicians' Health Study enrolled male patients without preexisting cardiovascular disease and found that aspirin was effective at preventing first myocardial infarction except among those who reported taking NSAIDs at least 60 days per year, where the risk of myocardial infarction was increased.²⁴ The mechanism for the harmful effect of NSAIDs could be that these agents interfere with the irreversible inhibition of cyclo-oxygenase-1 enzyme by aspirin because they compete for binding at the same site.^{25,26} This effect might be minimized by taking a nonselective NSAID at least 30 to 60 minutes after aspirin, or taking aspirin at least 8 hours after a short-acting nonselective NSAID.

The relationship between the primary outcome and mean systolic blood pressure between the study groups was similar except for very high systolic blood pressures. Chronic NSAID users appeared to be disproportionately harmed by markedly elevated blood pressure (systolic blood pressure >150 mm Hg); however, the level of uncertainty was high at this blood pressure level due to relatively few events.

Strengths

This observational study was conducted within a large randomized trial that provided long-term blood pressure measures, target blood pressures, and standardized assessment of adverse cardiovascular outcomes. Many of the previous analyses on this topic have been conducted from case-control studies. We did not find a difference in serious gastrointestinal bleeding events from chronic NSAID use, as might have been expected.^{27,28} While this was somewhat counterintuitive, chronic NSAID users likely started these medications before study enrollment, at which time major bleeding events could have occurred. Therefore, patients who remained on these medications into study enrollment had essentially demonstrated that they were able to tolerate them without adverse events. It also is possible that because bleeding was not a primary focus of this trial, some events might have been missed.

Limitations

We acknowledge several limitations of this study. As previously pointed out, we did not have information on the specific type of NSAIDs or doses that patients were taking. The Nurses' Health Study was conducted during a similar time period and found that naproxen or ibuprofen was used in the majority of patients; therefore, one might expect a similar proportionate use of these medications in the present study.²⁹ In a very limited sample of patients in the current study, the most commonly used NSAIDs were naproxen and ibuprofen. Diclofenac and celecoxib were reported in a small proportion of patients.

Long-term NSAID use might be a marker for chronic inflammatory conditions such as rheumatoid arthritis, which has been shown to independently predict adverse outcomes.³⁰ A more frequent indication for chronic NSAID use is osteoarthritis, which also is associated with an increased prevalence of most of the cardiovascular risk factors, including metabolic syndrome.^{31–33} We did not have baseline information on rheumatoid arthritis or osteoarthritis. In addition, other unknown patient characteristics make confounding by indication a possibility. A separate study documented a harmful association between NSAIDs and adverse events after controlling for rheumatoid arthritis and osteoarthritis.²⁹

The Kaplan-Meier curves appeared to converge late in follow-up. This was likely due to a variety of reasons. Events in chronic NSAID users occurred more rapidly than nonchronic NSAID users. Due to the smaller sample size of the chronic NSAID users, the Kaplan-Meier curve for that group becomes unstable late in follow-up. Given a long enough study time, all Kaplan-Meier curves will eventually converge when all patients have either experienced the event or become censored. In multivariate modeling, obesity and hypercholesterolemia appeared to have protective effects from adverse events. These paradoxes have been previously described and they deserve further study.^{34,35} Lastly, we considered the use of

NSAIDs at each follow-up visit as a proxy for daily use. It is possible that some of the patients categorized as chronic NSAID users were not daily users; however, this potential miscategorization would have posed more of a problem if no association was found with chronic NSAID use.

CONCLUSIONS

Among coronary artery disease patients with hypertension, chronic self-reported use of NSAIDs was associated with harmful outcomes, and this practice should be avoided where possible. This association did not appear to be due to elevated blood pressure because chronic NSAID users actually had slightly lower on-treatment blood pressure over a mean of 2.7 years of follow-up. Until further data are available, alternative modes of pain relief should be considered for these patients.

Acknowledgments

Funding: INVEST was funded by a grant from Abbott Laboratories and the University of Florida Opportunity Fund.

Dr. Handberg received grant support from the National Institutes of Health (NIH) (National Heart, Lung and Blood Institute [NHLBI]), Abbott Laboratories, Fujisawa, Pfizer, and GlaxoSmithKline. Dr. Cooper-DeHoff received research funding from Abbott Laboratories during the conduct of INVEST and is currently receiving funding from NIH (NHLBI) K23HL086558. Dr. Pepine received research grants from NIH (NHLBI), Baxter, Pfizer, GlaxoSmithKline, and Bioheart, Inc. and is a consultant for Abbott Laboratories, Forest Laboratories, Novartis/Cleveland Clinic, NicOx, Angioblast, Sanofi-Aventis, NHLBI, NIH, Medtelligence, and SLACK Inc. Drs. Handberg and Pepine have received educational grants from the Vascular Biology Working Group (AstraZeneca, Sanofi-Aventis, Schering-Plough, Daiichi-Sankyo Lilly, AtCor Medical, and XOMA).

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CLINICAL SIGNIFICANCE

- Chronic pain syndromes are commonly treated with long-term nonsteroidal anti-inflammatory drugs (NSAIDs).
- Many of these patients have underlying hypertension and coronary artery disease.
- Currently, there is a paucity of data about possible harmful effects of chronic NSAIDs in patients with hypertension and coronary artery disease.

Figure 1.

Systolic and diastolic blood pressure over time by nonsteroidal anti-inflammatory group. $P < .05$ for all time points, except for diastolic blood pressure at 30 months ($P = .12$) and 36 months ($P = .41$). NSAID = nonsteroidal anti-inflammatory drug.

Figure 2. Kaplan-Meier curves for the time (years) to first occurrence of the primary outcome by nonsteroidal anti-inflammatory group (adjusted hazard ratio = 1.47; 95% confidence interval, 1.19–1.82; $P = .0003$). NSAID = nonsteroidal anti-inflammatory drug.

Figure 3. Adjusted hazard ratios for the primary outcome in the 2 treatment groups as a function of mean systolic blood pressure. NSAID = nonsteroidal anti-inflammatory drug.

Table 1**Baseline Characteristics and Medications of the Study Population**

Baseline Characteristic	Chronic NSAIDs (n = 882)	Nonchronic NSAIDs (n = 21,694)	P Value
Age, mean years (SD)	65.3 (9.9)	66.1 (9.8)	.02
Age >70 years, %	29.7	33.5	.02
Women, %	66.9	51.5	<.0001
Race/ethnicity, %			<.0001
White	11.7	49.9	
African American	10.0	13.6	
Hispanic	75.5	34.0	
BMI, mean kg/m ² (SD)	29.5 (5.6)	29.2 (7.2)	.18
Blood pressure, mm Hg			
Systolic, mean (SD)	147.9 (19.9)	151.0 (19.5)	<.0001
Diastolic, mean (SD)	85.0 (10.5)	87.3 (12.0)	<.0001
History of, %			
Myocardial infarction	12.9	32.8	<.0001
Stable angina	90.7	65.7	<.0001
CABG or PCI	8.7	28.1	<.0001
Stroke or TIA	5.0	7.3	.009
LVH	19.2	22.0	.044
Arrhythmia	3.0	7.3	<.0001
HF (class I to III)	3.7	5.6	.016
Smoker, current	12.1	12.5	.78
Smoker, ever	51.9	46.1	.0006
Diabetes mellitus	33.1	28.2	.0014
Hypercholesterolemia	64.7	55.4	<.0001
Renal insufficiency	0.68	1.9	.0075
Peripheral arterial disease	26.5	11.4	<.0001
Medications, %			
Aspirin	46.9	57.1	<.0001
NSAIDs	100	14.4	<.0001
Diabetes medication	30.4	22.2	<.0001
Lipid-lowering medication	32.7	36.9	.01
Nitrates	71.3	34.6	<.0001
Hormone replacement	17.2	9.2	<.0001

BMI = body mass index; CABG = coronary artery bypass grafting; HF = heart failure; LVH = left ventricular hypertrophy; NSAIDs = nonsteroidal anti-inflammatory drugs; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

Table 2

Independent Predictors of the Primary Outcome

Variable	HR	95% CI	P Value
Chronic NSAID use	1.47	1.19–1.82	.0003
Percentage of visits with aspirin use	1.23	1.09–1.40	.0009
Age, per decade	1.63	1.56–1.72	<.0001
Men	1.11	1.01–1.21	.028
United States residency	1.65	1.43–1.89	<.0001
BMI, per 5 kg/m ²	0.88	0.84–0.92	<.0001
Hyperlipidemia	0.79	0.72–0.86	<.0001
Diabetes	1.75	1.60–1.91	<.0001
Current smoking	1.40	1.28–1.54	<.0001
PAD	1.25	1.12–1.40	<.0001
Renal insufficiency	1.49	1.22–1.81	<.0001
Prior:			
Myocardial infarction	1.36	1.24–1.48	<.0001
CABG or PCI	1.14	1.03–1.25	.0087
Heart failure	2.05	1.81–2.33	<.0001
Stroke or TIA	1.41	1.25–1.59	<.0001
Arrhythmia	1.16	1.02–1.33	.029
Mean on-treatment SBP*	1.06	1.04–1.08	<.0001
Mean on-treatment DBP*	1.05	1.02–1.08	.0033

BMI = body mass index; CABG = coronary artery bypass grafting; CI = confidence interval; DBP = diastolic blood pressure; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drug; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention; SBP = systolic blood pressure; TIA = transient ischemic attack.

* per 5 mm Hg.

Table 3

Event Rates for Adverse Cardiovascular Outcomes

Variable	Chronic NSAIDs (Events per 100 Pt-yrs)	Nonchronic NSAIDs (Events per 100 Pt-yrs)	Adjusted HR (95% CI)	P Value
Death, MI, stroke	4.4	3.7	1.47 (1.19–1.82)	.0003
All-cause mortality	4.3	2.8	1.89 (1.53–2.35)	<.0001
All-cause mortality (extended follow-up)*	3.1	2.4	1.24 (1.05–1.47)	.013
Cardiovascular mortality	2.4	1.4	2.26 (1.70–3.01)	<.0001
Fatal and nonfatal myocardial infarction	1.9	1.5	1.66 (1.21–2.28)	.0017
Fatal and nonfatal stroke	0.4	0.6	0.85 (0.43–1.65)	.63

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; NSAID = nonsteroidal anti-inflammatory drug; Pt-yrs = patient-years.

* US cohort of patients.