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Rates of Nonsteroidal Anti-Inflammatory Drug Use in Patients with Established Cardiovascular Disease: A Retrospective, Cross-Sectional Study from NHANES 2009–2010

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Abstract

Purpose—Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat pain, inflammation, and fever in the USA. Unfortunately, NSAIDs have been associated with an increased risk of adverse cardiovascular events, especially among NSAID users with established cardiovascular disease (CVD). In 2005, the Food and Drug Administration (FDA) released an initial warning regarding NSAID use and CVD risk, and recently, in July 2015, released an updated statement strengthening this initial warning. The purpose of this study is to evaluate the rates of NSAID use among patients with CVD following the 2005 FDA warning regarding NSAID use and increased CVD risk.

Methods—This was a retrospective, cross-sectional study of participants from the National Health and Nutrition Examination Survey, 2009–2010. Participants' CVD status was determined by self-reported diagnosis. Current use of over the counter (OTC) NSAIDs was defined by self-reported use of ibuprofen or naproxen, and we identified the current use of prescription NSAIDs in the database of prescription medication.

Results—Respondents with CVD were 2.1 times more likely to use OTC NSAIDs or prescription NSAIDs than respondents without CVD. Among CVD patients, respondents with angina and myocardial infarction were 60% more likely to use any form of NSAID, and respondents with congestive heart failure were less likely to use any form of NSAID than those with other forms of CVD.

Conclusions—Our results indicate that there is still a large proportion of CVD patients using NSAIDs. It is now crucial to determine the reasons why prescribers are still prescribing NSAIDs despite the FDA warning.

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Compliance with Ethical Standards

This was a retrospective analysis of publicly available de-identified data; therefore, no institutional review board approval was warranted for this study.

Conflict of interest All authors—Gregory Castelli, Ashley Petrone, Jun Xiang, Carl Shrader, and Dana King—declare that they have no conflict of interest that might be relevant to the contents of this article.

1 Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat pain, inflammation, and fever in the USA [1]. NSAIDs are widely available in over-the-counter (OTC) and prescription products. While effective for many indications, NSAIDs also carry risks associated with use, including gastrointestinal bleeding, hepatotoxicity, renal dysfunction, and cardiovascular disease (CVD) [2–11]. The risk of CVD is increased in patients with existing CVD including myocardial infarction (MI), unstable angina, heart failure, stroke, and peripheral vascular disease [9, 12–15]. Patients with established CVD may be unaware that NSAIDs should be avoided. Additionally, this subset of patients is more likely to use NSAIDs due to advanced age and multiple comorbid conditions.

NSAIDs have been shown to increase the risk of CVD in the general population and also in patients with established CVD. One potential mechanism might be NSAID-induced increased blood pressure in both normotensive and hypertensive patients [16, 17]. Additionally, NSAIDs inhibit cyclo-oxygenase (COX) throughout the body. COX and its products have a role in regulation of platelet activity and endothelial cells. Through COX suppression, cardiac smooth muscle cells may not relax and platelet aggregation is uninhibited [16]. Furthermore, NSAIDs can interfere with aspirin activity and decrease aspirin's beneficial effects for primary and secondary prevention of CVD [18–20]. While unclear, NSAIDs might also compete with aspirin for a common platelet binding site on COX-1, leading to increased platelet aggregation [21].

In 2005, the Food and Drug Administration (FDA) asked manufacturers of all prescription and OTC NSAIDs to revise labeling to include a boxed warning about the potential increased risk of CVD. Recently, in July 2015, the FDA issued an updated statement strengthening their previous 2005 warning [22]. This new warning was the result of FDA review of numerous clinical trials and safety data that emerged after 2005, leading to a revised prescription NSAID label that would more accurately reflect the risks of prescription NSAID use, particularly among patients with established CVD. The purpose of this study was to evaluate the rates of NSAID use among patients with CVD following the 2005 FDA warning regarding NSAID use and increased CVD risk.

2 Methods

2.1 Study Population

This was a retrospective, cross-sectional study of participants from the National Health and Nutrition Examination Survey (NHANES) 2009–2010. The NHANES is a series of complex and multistage surveys, which has been conducted regularly since the early 1960s by the Centers for Disease Control and Prevention (CDC) for the purpose of assessing the health and nutritional status of non-institutionalized US civilian residents. Participants aged 20–69 years who were not pregnant at the time of the NHANES 2009–2010 survey were eligible for inclusion. We analyzed survey data from the NHANES 2009–2010 survey only, as this is the most recent survey year to record data on OTC NSAID use.

2.2 Demographic Characteristics

Demographic characteristics including age, gender, race, and education level were obtained to evaluate the basic information of the study respondents.

2.3 Cardiovascular Disease (CVD)

Participants' CVD status was determined by self-reported diagnosis of at least one of the five following CVD subtypes: congestive heart failure (CHF), coronary artery disease (CAD), angina, MI, and stroke. The presence of CVD was defined by self-reported positive selection (yes or no) for at least one of these conditions, and CVD respondents could belong to more than one CVD subtype group.

2.4 Nonsteroidal Anti-Inflammatory Drug (NSAID) Use

OTC NSAID use was defined by self-reported use of ibuprofen or naproxen. We identified prescription NSAID users in the database of prescription medication, and 30 medications were included in the list of prescription NSAIDs (Table 1). As shown, aspirin and acetaminophen were excluded from the list of NSAIDs. Respondents who reported use of at least one prescription NSAID, regardless of duration of use, were identified as prescription NSAID users. The duration of prescription NSAID use was recorded for each prescription NSAID, and maximum duration of NSAID use of 1 year or longer was considered long-term use. For respondents using more than one prescription NSAID, we used the longest duration of use among the list of prescription NSAIDs to determine long-term use.

2.5 Statistical Analysis

Statistical analysis software (SAS version 9.3, 2012, SAS institute Inc., Cary, NC, USA) was used for all statistical analyses, and statistical significance was set at $p < 0.05$. Unweighted demographic characteristics and NSAID use were calculated. The differences between respondent characteristics and NSAID use were compared using Chi-square analysis. To account for the complex survey design (including oversampling), survey nonresponse, and post-stratification, all comparisons were weighted using the 2-year interview sample weights provided by the CDC. To adjust for the effects of the demographic covariates, logistic regression was performed to further examine the relationship between current NSAID use and the status of CVD.

3 Results

3.1 Sample Characteristics

Based on the inclusion criteria, a total of 5058 respondents [330 (6.5%) with CVD and 4728 (93.5%) without CVD] were included in this study. The demographic characteristics of respondents are summarized in Table 2. Respondents with CVD (mean age 57 ± 10 years) were significantly older than respondents free of CVD (mean age 43 ± 14 years) ($p < 0.001$). There was also a significantly higher proportion of males in the CVD group than in those free of CVD ($p < 0.001$). Further, there was a slight group difference in the racial profile of respondents, as there was a significantly greater number of Hispanic participants represented

in the CVD group ($p = 0.003$). Lastly, there were significantly more respondents that did not complete high school in the CVD group compared with the non-CVD group ($p < 0.001$).

3.2 NSAID Use Between Respondents with or Without CVD

As shown in Table 3, among the sample population of 5058 respondents, the total rate of NSAID use (any form) was nearly 25%. Of this population of total NSAID users, 89% reported OTC NSAID use, 21% reported prescription NSAID use, and 10% reported concurrent use of OTC and prescription NSAIDs. Further, of the total population using prescription NSAIDs, 54% reported using at least prescription NSAID for a duration of 1 year or longer (Table 3).

Reported total NSAID use was significantly higher in the CVD group (43%) than in the non-CVD group (24%) ($p < 0.001$). Further, respondents with CVD were 2.1 times more likely to use any form of NSAID than respondents without CVD (Table 4). Both reported OTC NSAID use (38%; $p < 0.001$) and prescription NSAID use (10%; $p < 0.001$) were significantly higher among respondents with CVD compared with those without CVD (22 and 4%, respectively) (Table 3). Respondents with CVD were 2.1 times more likely to use OTC NSAIDs and 2.1 times more likely to use prescription NSAIDs than respondents without CVD (Table 4). Similarly, concurrent OTC and prescription NSAID use was significantly higher in the CVD group (6%) compared with those without CVD (2%) ($p < 0.001$) (Table 3). Lastly, all of these differences in NSAID use between the CVD and non-CVD groups remain significant following logistic regression analysis controlling for age, sex, race, and education ($p < 0.001$). In the respondents who reported prescription NSAID use, there was no significant difference in the number of respondents who used at least one prescription NSAID for a duration greater than 1 year between respondents with CVD (54%) and without CVD (46%) ($p = 0.64$) (Table 3).

3.3 NSAID Use Among CVD Subtypes

Next, we examined reported NSAID use among the CVD group alone, comparing NSAID use among the different CVD subtypes. The self-reported prevalence rates of each CVD subtype among respondents with CVD were as follows: 2.4% CHF, 36% CAD, 24% angina, 42% MI, and 35% stroke (not shown). Table 5 summarizes the reported use of NSAIDs of all forms by CVD subtype. The rates of total NSAID, OTC NSAID, prescription NSAID, and concurrent NSAID use are highest in CVD respondents with angina and MI compared with those with other forms of CVD. Respondents with angina and MI were 60% more likely to use any form of NSAID (Table 4). Respondents with MI are 60% more likely and respondents with angina are 40% more likely to use OTC NSAIDs than respondents with other forms of CVD (Table 4). Respondents with CHF were less likely to use any form of NSAID than those with other forms of CVD (Table 4).

4 Discussion

The purpose of this study was to evaluate the rates of NSAID use among patients with CVD following the 2005 FDA warning regarding NSAID use and increased CVD risk. Here, we have shown that according to 2009–2010 NHANES data, rates of NSAID use are higher

among patients with CVD than those without. CVD patients are more likely to use both prescription and OTC NSAIDs than those without CVD, and 66% of CVD patients reported using at least one prescription NSAID for 1 year or longer. Lastly, among CVD subtypes, total NSAID use was highest among patients with angina and lowest among patients with stroke.

There has been ample evidence to support the association of increased risk of CVD and NSAID use, especially among individuals with pre-existing CVD [22], despite the fact that the definite physiological mechanisms by which NSAID drugs may trigger a cardiovascular event remain elusive [22]. There have been few studies examining the overall rates of NSAID use in the USA following the initial FDA warning in 2005, and none that have provided an estimated rate of NSAID use among patients with pre-existing CVD. One 2012 study showed that the rate of potentially inappropriate medication prescriptions, which include NSAIDs, has decreased from 45.5% in 2006–2007 to 40.8% in 2009–2010 [23]. Further, prevalence of NSAID prescriptions showed the largest decline compared with other drug categories [23]. While this may indicate that prescribers and patients heeded the initial 2005 FDA warning, our results indicate that there is still a large proportion of CVD patients using NSAIDs. Considering the updated statement in July 2015 strengthening the previous warning regarding NSAIDs, it will be important to provide a rate of NSAID use prior to this updated statement. Based on 2009–2010 NHANES data, we have shown that roughly 25% of the overall population and 43% of the CVD populations are using a form of NSAID. While the rate in the overall population may not be troubling to some, the high prevalence of NSAID use in CVD patients must be addressed.

4.1 Limitations

Our study has several limitations that need to be addressed. First, despite the use of the large NHANES database, the number of responders with CVD was remarkably low at 330 respondents. Thus, while NHANES is conducted to obtain responses from a random population sample representative of the US population as a whole, the rates we described in this study may not be applicable to the US population as a whole. More importantly, because of this small sample size, we were limited in our ability to analyze this data split into groups of interest. Second, the data used in this study are derived from the years 2009–2010. While this data provides an accurate depiction of a time point following the initial 2005 FDA warning, there is no reported rate of NSAID use for comparison. We chose to use the 2009–2010 NHANES dataset, as opposed to any data from 2006–2009, because the 2009–2010 NHANES dataset was the most recent dataset that recorded OTC NSAID use. Considering that the rate of OTC NSAID use was much higher both overall and in CVD patients, we rationalized that OTC rates would provide more clinical relevance than prescription NSAIDs alone. Lastly, the comparison of NSAID use among CVD subtypes was conducted in a relatively small sample; thus our results need to be interpreted as evocative in nature, and future studies should address NSAID use among difference CVD subtypes in a larger sample.

4.2 Future Directions

Our study has provided a reference point, as well as raised several important clinical questions that may be addressed in future research. First, future studies with a larger sample of CVD patients may help answer more specific questions regarding NSAID use in this population. Future studies will be crucial to address the types of NSAIDs that are commonly used among CVD patients, as well as the different rates of NSAID use among those with different CVD subtypes and duration of CVD. Based upon these results, it will be vital to determine the reasons why NSAID use remains high in patients with CVD and if there are specific CVD patients in whom the benefits of NSAID use outweigh the increased risk of a CV event. For example, given the recent 2015 FDA warning, it will be interesting to measure the change in the prevalence of NSAID use prior to 2015 and after 2015. Lastly, it is also important to reinforce strategies, to both clinicians and patients, that can be used to reduce NSAID reliance altogether and improve safety if NSAID use is warranted, such as prescribing NSAIDs at the lowest effective dose, only prescribing one NSAID at a time, limiting the duration of NSAID use, or using alternative medications, such as acetaminophen.

Because the NHANES 2016–2017 national data will not be made publicly available for several years, it may be timelier to conduct smaller scale studies to measure the rate of NSAID use in the overall and CVD population. We are currently conducting a study among family medicine clinics in West Virginia to address the limitations in this study and target the mentioned future directions.

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Abbreviations

CVD	Cardiovascular disease
CDC	Centers for Disease Control and Prevention
CAD	Coronary artery disease
CHF	Congestive heart failure
COX	Cyclo-oxygenase
FDA	Food and Drug Administration
MI	Myocardial infarction
NHANES	National Health and Nutrition Examination Survey
NSAIDs	Nonsteroidal anti-inflammatory drugs
OTC	Over-the-counter

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Key Points

Both over-the-counter nonsteroidal anti-inflammatory drug (NSAID) use and prescription NSAID use are significantly higher in patients with cardiovascular disease (CVD) than in patients free of CVD.

Among patients with CVD, total NSAID use was highest among CVD patients with angina and lowest among CVD patients with stroke.

Future research is needed to address the reasons why NSAID use remains high in CVD patients, despite Food and Drug Administration (FDA) warnings, and to develop strategies to reduce NSAID reliance.

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Table 1

List of included NSAIDs (drug code and generic prescription name)

Drug codes	Generic prescription name
d00033	Sulindac
d00853	Oxaprozin
d00842	Salsalate
d00208	Diflunisal
d00343	Piroxicam
d00039	Indomethacin
d00851	Etodolac
d00019	Naproxen
d07130	Naproxen; sumatriptan
d00310	Nabumetone
d00848	Diclofenac
d04722	Diclofenac topical
d00015	Ibuprofen
d00028	Ketoprofen
d00273	Ketorolac
d00026	Fenoprofen
d00239	Flubiprofen
d00285	Mefenamic acid
d00054	Tolmetin
d04433	Rofecoxib
d04778	Valdocoxib
d04532	Meloxicam
d04380	Celecoxib
d00283	Meclofenamate
d04913	Lansoprazole; naproxen
d04225	Hydrocodone; ibuprofen
d04271	Diclofenac; misoprostol
h00029	Carisoprodol; diclofenac
h00022	Tiaprofenic acid
h00027	Acetaminophen; naproxen

NSAID nonsteroidal anti-inflammatory drug

Table 2Unweighted socio-demographic characteristics of study population from NHANES 2009–2010 ($n = 5058$)

	Overall ($n = 5058$)	CVD ($n = 330$)	Non-CVD ($n = 4728$)	p value[*]
Age (mean $\pm$ SD years)	44.0 $\pm$ 14.1	56.5 $\pm$ 10.2	43.1 $\pm$ 13.9	<0.001
Sex (%)				<0.001
Male	48.9	59.1	48.2	
Female	51.1	40.9	51.8	
Race (%)				0.02
White	44.1	44.6	44.0	0.27
Black	18.9	24.9	18.5	0.07
Hispanic	31.3	26.1	31.7	0.003
Other	5.7	4.6	5.8	0.25
Education (%)				0.001
Did not complete high school	27.1	37.9	26.3	
Completed high school	72.9	62.1	73.7	

CVD cardiovascular disease, *NHANES* National Health and Nutrition Examination Survey, *SD* standard deviation

^{*} p values for all weighted comparison across CVD status, by regression analysis (continuous variables) and Chi-square analysis (categorical variables). Bolded values highlight $p < 0.05$

Table 3Prevalence of reported NSAID use by CVD status in NHANES 2009–2010 ($n = 5058$)

No. (%) respondents	Overall	CVD	Non-CVD	<i>p</i> value*
Total NSAID	1277 (24.9)	142 (41.9)	1135 (23.9)	<0.001
OTC NSAID	1141 (22.6)	122 (38.0)	1019 (21.8)	<0.001
Prescription NSAID	269 (4.5)	41 (10.1)	228 (4.2)	<0.001
Long-term NSAID	140 (47.0)	26 (53.6)	114 (46.1)	0.64
Concurrent OTC and prescription NSAID	133 (2.2)	21 (6.2)	112 (2.0)	<0.001

NSAID use categories: total NSAID = prescription or OTC NSAID use; OTC NSAID = OTC NSAID use; prescription NSAID = prescription NSAID use; long-term NSAID = prescription NSAID use for 1 year or longer; concurrent OTC and prescription NSAID = both OTC and prescription NSAID use *CVD* cardiovascular disease, *NSAID* nonsteroidal anti-inflammatory drug, *NHANES* National Health and Nutrition Examination Survey, *OTC* over-the-counter

*
 p values for Chi-square analysis comparing difference of NSAID prevalence by CVD status. Bolded values highlight $p < 0.05$

Table 4

Logistic regression estimates for comparing the prevalence of NSAID use by CVD status controlling for socio-demographic characteristics

NSAID use	CVD		CHF		CAD		Angina		MI		Stroke	
	OR ^a	95% CI	OR ^a	95% CI	OR ^a	95% CI	OR ^a	95% CI	OR ^a	95% CI	OR ^a	95% CI
Total NSAID	2.1	1.5–3.0	0.8	0.4–1.5	0.7	0.4–1.2	1.6	0.9–2.6	1.6	0.9–2.7	0.5	0.3–0.8
OTC NSAID	2.1	1.5–2.9	0.8	0.4–1.6	0.6	0.3–1.3	1.4	0.8–2.4	1.6	0.9–2.8	0.6	0.3–0.9
Prescription NSAID	2.1	1.2–3.6	0.4	0.1–0.9	0.6	0.3–1.2	1.3	0.5–3.0	2.1	1.2–3.7	0.3	0.1–0.8
Concurrent OTC and prescription NSAID	2.7	1.4–5.1	0.2	0.1–0.9	0.2	0.04–1.1	0.9	0.2–3.3	3.2	1.5–6.9	0.6	0.2–1.6

NSAID use categories: total NSAID = prescription or OTC NSAID use; OTC NSAID = OTC NSAID use; prescription NSAID = prescription NSAID use; concurrent OTC and prescription NSAID = both OTC and prescription NSAID use

CAD coronary artery disease, CHF congestive heart failure, CI confidence interval, CVD cardiovascular disease, MI myocardial infarction, NSAID nonsteroidal anti-inflammatory drug, OR odds ratio, OTC over-the-counter

^aOR from logistic regression analysis, testing the association between NSAID use and CVD status and CVD subtype controlling for socio-demographic characteristics

Table 5Prevalence of reported NSAID use by CVD subtype in NHANES 2009–2010 (*n* = 330)

CVD subtype	Total NSAID		OTC NSAID		Prescription NSAID		Concurrent OTC and prescription NSAID	
	<i>n</i> (%)	<i>p</i> value*	<i>n</i> (%)	<i>p</i> value*	<i>n</i> (%)	<i>p</i> value*	<i>n</i> (%)	<i>p</i> value*
CHF								
Yes	33 (36.8)	0.47	28 (33.9)	0.53	7 (4.9)	0.10	2 (2.0)	0.05
No	107 (43.3)		92 (39.1)		34 (11.7)		19 (7.5)	
CAD								
Yes	45 (36.4)	0.23	36 (30.5)	0.12	12 (8.2)	0.41	3 (2.3)	0.09
No	96 (45.2)		85 (42.4)		29 (11.2)		18 (8.4)	
Angina								
Yes	46 (50.5)	0.10	40 (44.5)	0.23	13 (11.7)	0.63	7 (5.8)	0.86
No	95 (39.1)		81 (35.9)		28 (9.6)		14 (6.4)	
MI								
Yes	65 (46.8)	0.19	59 (43.3)	0.16	18 (13.5)	0.03	12 (10.0)	0.009
No	76 (38.2)		62 (34.0)		23 (7.4)		9 (3.2)	
Stroke								
Yes	37 (32.3)	0.04	35 (31.7)	0.11	8 (5.0)	0.02	6 (4.5)	0.36
No	105 (46.6)		87 (41.1)		33 (12.5)		15 (7.0)	

NSAID use categories: total NSAID = prescription or OTC NSAID use; OTC NSAID = OTC NSAID use; prescription NSAID = prescription NSAID use; concurrent OTC and prescription NSAID = both OTC and prescription NSAID use

CAD coronary artery disease, CHF congestive heart failure, CVD cardiovascular disease, MI myocardial infarction, NSAID nonsteroidal anti-inflammatory drug, NHANES National Health and Nutrition Examination Survey, OTC over-the-counter

* *p* values for Chi-square analysis comparing difference of NSAID prevalence by CVD subtype. Bolded values highlight *p* < 0.05