Received: 25 September 2020 | Revised: 5 November 2020 | Accepted: 6 November 2020

DOI: 10.1002/phar.2488

PHARMACOTHERAPY accp

ORIGINAL RESEARCH ARTICLE

U.S. trends in prescription nonsteroidal anti-inflammatory drug use among patients with cardiovascular disease, 1988–2016

Andrew Y. Hwang[1] | Steven M. Smith[2]

[1]Department of Clinical Sciences, Fred Wilson School of Pharmacy, High Point University, High Point, North Carolina, USA

[2]Departments of Pharmacotherapy and Translational Research and Pharmaceutical Outcomes and Policy, College of Pharmacy, and Center for Integrative Cardiovascular and Metabolic Disease, University of Florida, Gainesville, Florida, USA

Correspondence
Andrew Y. Hwang, Department of Clinical Sciences, Fred Wilson School of Pharmacy, High Point University, One University Parkway, High Point, NC 27268, USA.
Email: ahwang@highpoint.edu

Funding information
Dr. Smith is funded by the National Heart, Lung and Blood Institute (K01 HL138172).

Abstract

Background: Nonsteroidal antiinflammatory drugs (NSAIDs) have been associated with increased risk of adverse cardiovascular events prompting labeling revisions cautioning their use among patients with cardiovascular disease (CVD). However, little is known regarding long-term trends in real-world prescribing of NSAIDs within the CVD population. We aimed to characterize the use of prescription NSAIDs among U.S. adults with CVD from 1988 to 2016.

Methods: We used the National Health and Nutrition Examination Survey cross-sectional data from 1988–1994 and 19992016 to identify participants aged greater than or equal to 18 years with hypertension (defined by self-report, mean blood pressure ≥ 140/90 mm Hg, or antihypertensive medication use), or aged greater than or equal to 20 years with self-reported congestive heart failure (CHF), coronary heart disease (CHD), angina, myocardial infarction (MI), or stroke. Prevalence of prescription NSAID use was analyzed in 6-year examination periods. Weighted logistic regression was performed to test time trends in prescription NSAID use.

Results: Overall, prescription NSAID use declined among all CVD populations. The highest prevalence of overall prescription NSAID use was observed during the 1999–2004 examination years, thereafter declining through the 2005–2010 and 2011–2016 examination years: in patients with hypertension (13.9% [1999–2004] to 8.5% [2011–2016]), CHF (14.6%–8.5%), CHD (16.3%–7.4%), angina (17.6%–8.5%), MI (16.1%–9.0%), and stroke (15.7%–7.9%). Decreased use of COX-2-selective inhibitors was observed during the same period; whereas, nonselective NSAID use remained relatively stable. Trends in prescription NSAID use were reflective of the general adult population.

Conclusions: Prescription NSAID use among patients with CVD appears to have declined from 1988 to 2016, primarily due to reduced COX-2-selective inhibitor use. Nonetheless, the prevalence of prescription NSAIDs has persisted among a subset of high-risk CVD populations.

KEYWORDS
cardiovascular disease, nonsteroidal antiinflammatory drugs, trends

1 | INTRODUCTION

Nonsteroidal antiinflammatory drugs (NSAIDs) are commonly prescribed to treat minor pain, fever, or inflammation. Available over-the-counter (OTC) and by prescription, the ubiquitous use of NSAIDs has led to concerns about the increased risk of adverse cardiovascular events, particularly in patients with established cardiovascular disease (CVD).[1–3] In 2005, the U.S. Food and Drug

Administration (FDA) suggested labeling revisions for all NSAIDs to warn about the potential increased risk of adverse cardiovascular events. Subsequently, in July 2015, the FDA issued an updated statement that strengthened their previous warning, based on safety data suggesting increased risk of myocardial infarction (MI) and stroke among patients with preexisting CVD.[4] Furthermore, contemporary guidelines have recognized the potential of NSAIDs to interfere with management of hypertension and heart failure, and recommendations have been issued to encourage avoidance of NSAIDs in these populations.[5,6]

Despite these recommendations to limit NSAID use in high risk populations, the prevalence of NSAID use among patients with CVD is incompletely understood. Prior studies have estimated the use of NSAIDs within the overall U.S. population to be ~12%[7,8]; and only recently have studies underscored a relatively high prevalence among patients with established CVD.[9–11] Little is still known regarding the long-term trends in NSAID use within the CVD population, particularly as it pertains to the issuance of the FDA warnings. Therefore, we aimed to characterize the trends in the use of prescription NSAID among patients with CVD from 1988 to 2016. Specifically, we focused our investigation on analyzing NSAID use among CVD populations in which NSAIDs should be minimized to the extent possible, due to increased adverse cardiovascular risk.

2 | METHODS

2.1 | Study population

We used cross-sectional National Health and Nutrition Examination Survey (NHANES) data to examine the use of prescription NSAIDs among six CVD cohorts: patients with hypertension, congestive heart failure (CHF), coronary heart disease (CHD), angina, MI, and stroke. NHANES uses a complex sampling design to survey the health and nutritional status of both adults and children in the United States.[12] The surveys are carried out in a population-based cluster with random selection to identify a nationally representative sample. Information collected includes self-reported data (e.g., demographic, socioeconomic, dietary, and health-related behaviors), physical examinations, laboratory tests, and prescription medications. These datasets are publicly available through the Centers for Disease Control and Prevention (CDC), and do not contain any patient identifiers. This study was considered exempt from human subject research from the institutional review board at High Point University.

Adult participants aged greater than or equal to 18 years from NHANES III (1988–1994) and the continuous NHANES cycles (1999–2016) were eligible for the study. Specific CVD cohorts were identified among participants aged greater than or equal to 18 years with hypertension or aged greater than or equal to 20 years with established CVD. Hypertension was defined as either (a) self-reported diagnosis of hypertension on two or more office visits, or (b) mean systolic blood pressure (BP) greater than or equal to 140 mm Hg, mean diastolic BP greater than or equal to 90 mm Hg, or self-reported use of prescription medication for hypertension. Established CVD was determined through self-reported affirmative response for at least one of the following conditions: CHF, CHD, angina, MI, or stroke. Participants were grouped into six nonmutually exclusive CVD cohorts – hypertension, CHF, CHD, angina, MI, and stroke.

2.2 | NSAID exposure

Participants were identified as a prescription NSAID user if they reported use of at least one prescription NSAID, regardless of duration of use. Prescription NSAID information was obtained from the Prescription Medication Questionnaire using the generic drug codes provided by NHANES. We used the Drug Information File to create a list of prescription NSAIDs; the final list consisted of 32 unique generic drug codes (Table S1). NHANES does not distinguish between systemic formulations, therefore, the final list included all prescription NSAIDs regardless of formulation. Aspirin was excluded from the list because low-dose aspirin is indicated for secondary prevention in patients with established CVD. We also excluded topical diclofenac because topical formulations of NSAIDs are often recommended as preferred alternatives to systemic NSAIDs due to their low systemic absorption.

2.3 | Analysis

Because prescribing patterns may be affected by the type of CVD, we analyzed NSAID use stratified by specific CVD subtype. Trends in prescription NSAID use within each CVD cohort were analyzed in 6-year examination periods to improve statistical precision (i.e., NHANES III [1988–1994] and continuous NHANES cycles [1999–2004, 2005–2010, and 2011–2016]). Due to the lack of self-reported CHD and angina data in NHANES III, analysis of CHD and angina cohorts were restricted to continuous NHANES cycles only. Prescription NSAID use was also assessed within the general adult population, defined as aged greater than or equal to 18 years, to provide a perspective of the trends in context of the overall U.S. adult population. Prevalence estimates for prescription NSAID use were calculated using 6-year sample weights to account for the complex survey design. Estimates were assessed for overall prescription NSAIDs, nonselective NSAIDs, and COX-2-selective inhibitors. The modified Clopper-Pearson method was used to calculate 95% confidence intervals for prevalence estimates. Population counts of NSAID users were calculated by multiplying prevalence estimates with the Current Population Surveys-based population totals provided by the National Center for Health Statistics. Weighted logistic regression was performed to test time trends from 1988–2016, using time as an independent, continuous variable. The midpoint of the NHANES examination periods were designated for the model as follows: 1991 was used for 1988–1994, 2002 was used for 1999–2004, 2008 was used for

2005–2010, and 2014 was use for 2011–2016. Additionally, predictors of prescription NSAID use were examined using weighted multiple logistic regression using the continuous NHANES cycles combined into an 18-year period (1999–2016). Reference groups used in the regression analysis were patients without the relevant CVD. A single regression model was developed for each dependent variable (i.e., overall NSAIDs, nonselective NSAIDs, and COX-2-selective inhibitors), in which each individual CVD subtype was included as an independent variable. The regression model was also adjusted for the following covariates: age, sex, race/ethnicity, body mass index, self-reported health status, smoking status, self-reported chronic obstructive pulmonary disease (COPD), self-reported arthritis, and chronic kidney disease (CKD). The estimated glomerular filtration rate (eGFR), calculated by the modification of diet in renal disease equation, was used to categorize CKD severity as mild (eGFR ≥ 60 ml/min/1.73 m^2 with urinary albumin-to-creatinine ratio ≥30 mg/g) or moderate to severe (eGFR < 60 ml/min/1.73 m^2, regardless of albumin-to-creatinine ratio). All analyses were done using SAS version 9.4 (SAS Institute).

3 | RESULTS

3.1 | Cohort characteristics

Characteristics of the study populations are summarized by NHANES 6-year periods in the individual CVD cohorts (Table 1). Among participants in the hypertension cohort, demographic characteristics (i.e., age, gender, and race/ethnicity) remained largely consistent across NHANES periods. Overall, approximately half of patients with hypertension were aged greater than or equal to 60 years and slightly more than half were women. An increasing trend in the proportion of self-reported history of diabetes and arthritis was observed from the 1988–1994 to 2011–2016 examination periods, whereas the proportion with established CVD remained stable throughout the study period.

Among participants in the established CVD cohorts, the demographic characteristics and comorbidities remained largely consistent during the study period. Across all CVD cohorts, large majorities of patients were aged greater than or equal to 60 years. Approximately half of the patients in the CHF, angina, and stroke cohorts were women, whereas a majority of patients in the CHD and MI cohorts were men. Compared with the hypertension cohort, patients with established CVD were older and had higher prevalence of moderate to severe CKD and arthritis.

3.2 | Prevalence of NSAID use

The estimated prevalence and population counts of prescription NSAID use among each cohort are displayed and summarized in Figure 1 and Table S2. A consistent increase in prevalence of prescription NSAID use was noted from 1988–1994 to 1999–2004 among the hypertension, CHF, MI, and stroke cohorts. The highest prevalence of prescription NSAID use among all CVD cohorts was observed during the 1999–2004 examination period. Thereafter, use of prescription NSAIDs sharply declined during the 2005–2010 examination period. This trend was consistent across all six CVD cohorts: overall prescription NSAID use among adults with hypertension (13.9% [1999–2004] to 8.8% [2005–2010]), CHF (14.6%–8.5%), CHD (16.3%–7.0%), angina (17.6%–9.7%), MI (16.1%–8.2%), and stroke (15.7%–8.8%). Prescription NSAID use remained generally stable from the 2005–2010 to 2011–2016 examination periods; at which point, prescription NSAID users represented ~7 million adults with hypertension, 509 thousand adults with CHF, 571 thousand adults with CHD, 417 thousand adults with angina, 678 thousand adults with MI, and 512 thousand adults with stroke (Table S2). The overall results were reflective of the trends seen within the general adult population. Overall prevalence of prescription NSAIDs was similar across CVD cohorts but was notably higher than the general adult population (Figure S1).

In analyses stratified on NSAID type, prescription nonselective NSAID use remained consistent among all CVD cohorts from 1999–2004 to 2011–2016 examination periods. Conversely, the prevalence of COX-2-selective inhibitors decreased substantially from the 1999–2004 to 2005–2010 examination periods and remained consistently low during the 2011–2016 examination period. This trend was observed in all CVD cohorts: prevalence of COX-2-selective inhibitors use in adults with hypertension (6.7% [1999–2004] to 1.3% [2011–2016]), CHF (8.6%–1.5%), CHD (9.1%–1.0%), angina (9.5%–0.7%), MI (8.5%–0.2%), and stroke (5.7%–0.6%). Sensitivity analysis of 2-year continuous NHANES study periods showed similar trends for overall prescription NSAIDs, nonselective NSAIDs, and COX-2-selective inhibitors (Tables S3 and S4).

3.3 | Predictors of NSAID use by CVD status

Table 2 and Table S5 summarize predictors of prescription NSAID use by CVD status. Compared with patients without hypertension, patients with hypertension were more likely to be prescribed any NSAID (adjusted odds ratio [aOR], 1.27; 95% confidence interval [CI], 1.13–1.42) and nonselective NSAIDs (aOR 1.26; 95% CI, 1.09–1.45). In contrast, CHF was associated with decreased likelihood of using any prescription NSAIDs (aOR, 0.73; 95% CI, 0.56–0.96) and nonselective prescription NSAIDs (aOR, 0.70; 95% CI, 0.50–0.97) compared with patients without CHF. No significant associations were observed for use of overall prescription NSAIDs or nonselective prescription NSAIDs with the presence of CHD, angina, MI, or stroke. COX-2-selective inhibitor use was less likely among patients with stroke (aOR, 0.60; 95% CI, 0.39–0.92); however, no significant associations were seen with the other CVDs.

4 | DISCUSSION

Over the past 2 decades, increasing evidence of cardiovascular risk associated with NSAIDs has spurred labeling changes by the

TABLE 1 Characteristics (weighted) of General Adult Population and Adult Population With Cardiovascular Diseases, Stratified by NHANES Study Periods

	General adult population				Hypertension			
	NHANES study period				NHANES study period			
	1988–1994	1999–2004	2005–2010	2011–2016	1988–1994	1999–2004	2005–2010	2011–2016
Sample *n* (weighted *N*)	19,255 (180,859,529)	17,061 (208,576,407)	18,318 (222,364,573)	17,969 (236,631,221)	5602 (48,956,694)	5510 (65,532,074)	6503 (72,742,902)	6564 (82,185,578)
Age, yrs								
≤ 39	48.1%	41.8%	39.6%	38.2%	18.6%	13.4%	12.5%	12%
40–59	30.1%	36.5%	37.4%	35.8%	33.4%	39.7%	39.8%	38.2%
≥ 60	21.8%	21.7%	22%	26%	48%	46.9%	47.7%	49.8%
Female	52.2%	52%	51.7%	51.8%	52.7%	53.7%	51.9%	52%
Race/ethnicity								
NH White	76.2%	70.7%	69.4%	64.9%	77.7%	73.6%	72.3%	68.1%
NH Black	11.1%	11%	11.5%	11.6%	13.5%	13.2%	14.4%	14.3%
Mexican American	5.2%	7.4%	8.4%	8.8%	3.5%	4.4%	5.2%	6%
Other	7.5%	10.9%	10.7%	14.7%	5.3%	8.8%	8.1%	11.6%
Comorbidities								
Diabetes	5.3%	6.7%	8%	9.7%	11.4%	14.6%	17.4%	20.6%
Hypertension	27.1%	31.5%	32.7%	34.7%	–	–	–	–
Established CVD								
CHF	2.2%	2.4%	2.3%	2.6%	5.6%	5.1%	5.3%	6%
CHD	–	3.5%	3.3%	3.4%	–	8%	7.2%	7.3%
Angina	–	3.1%	2.2%	2.1%	–	6.8%	4.9%	4.6%
MI	3.5%	3.6%	3.3%	3.3%	8.1%	7.4%	7%	7.1%
Stroke	2.1%	2.6%	2.9%	2.8%	4.9%	6%	6.6%	6.2%
CKD								
Mild	8.3%	7.2%	7%	7.6%	13.7%	11.4%	10.9%	11.5%
Moderate-to-severe	10.4%	7.9%	7.9%	8.5%	18.7%	18%	17.7%	17.4%
Arthritis	17.7%	22.5%	24.6%	25.4%	33.2%	39.3%	41.6%	43.1%

(Continues)

TABLE 1 (Continued)

	CHF				CHD		
	NHANES study period				NHANES study period		
Characteristic	1988–1994	1999–2004	2005–2010	2011–2016	1999–2004	2005–2010	2011–2016
Sample *n* (weighted *N*)	745 (4,019,583)	551 (4,776,651)	571 (4,948,551)	583 (5,956,565)	707 (7,068,591)	707 (6,995,516)	672 (7,703,503)
Age, yrs							
≤ 39	5.3%	4.6%	4%	4.4%	2.4%	2.4%	2.3%
40–59	21.6%	27.5%	22.8%	21.6%	28.3%	23.2%	18.2%
≥ 60	73.1%	67.9%	73.2%	74%	69.3%	74.4%	79.5%
Female	50.5%	49.5%	45.1%	52.7%	37.3%	31.6%	39.5%
Race/ethnicity							
NH White	73.8%	77%	71.5%	68.7%	84.4%	82.1%	76.8%
NH Black	12.6%	11.5%	16.9%	15.2%	6.5%	6.2%	7.7%
Mexican American	5.3%	3.3%	3.4%	5.5%	2.5%	4.5%	3.7%
Other	8.3%	8.2%	8.2%	10.6%	6.6%	7.2%	11.8%
Comorbidities							
Diabetes	25.9%	30.6%	38.4%	39%	24.4%	30.4	34.3%
Hypertension	70.4%	70.8%	77.5%	82.7%	71.4%	74.5%	76.7%
Established CVD							
CHF	–	–	–	–	29.5%	26.5%	30.4%
CHD	–	44.6%	38.1%	39.9%	–	–	–
Angina	–	34.1%	24.9%	23.8%	44%	34.8%	32.6%
MI	55.2%	46.6%	45.7%	40.4%	53.6%	50.1%	48.8%
Stroke	19.2%	17.9%	21.5%	20.2%	13.6%	15.5%	15.5%
CKD							
Mild	12.5%	12.9%	12.3%	15.9%	11.9%	12.3%	12.2%
Moderate-to-severe	38.3%	40.6%	39.4%	42.6%	29.6%	29.7%	33.7%
Arthritis	56.4%	60.7%	58.5%	61.2%	53.4%	54.1%	57.9%

(Continues)

TABLE 1 (Continued)

	Angina			MI			
	NHANES study period			NHANES study period			
Characteristic	1999–2004	2005–2010	2011–2016	1988–1994	1999–2004	2005–2010	2011–2016
Sample *n* (weighted *N*)	591 (6,122,343)	474 (4,635,956)	398 (4,920,041)	928 (6,266,263)	753 (7,200,724)	758 (7,118,892)	684 (7,538,112)
Age, yrs							
≤ 39	3%	4%	4.6%	3.1%	3.1%	4.5%	2.7%
40–59	34.1%	27.1%	28.7%	24.2%	29.8%	28.8%	26.1%
≥ 60	62.9%	68.9%	66.7%	72.7%	67.1%	66.7%	71.2%
Female	48.4%	45.6%	48.2%	37.7%	37.4%	36.1%	40.4%
Race/ethnicity							
NH White	83.9%	77.6%	79.7%	84.2%	81.9%	79%	74.1%
NH Black	5.5%	8.8%	7.9%	8.9%	9.1%	10.1%	9.4%
Mexican American	2.9%	5.4%	3.5%	2.5%	2.7%	3.7%	4.5%
Other	7.7%	8.2%	8.9%	4.4%	6.3%	7.2%	12%
Comorbidities							
Diabetes	23.9%	31.3%	36.8	20.6%	22.6%	28.7%	33.5%
Hypertension	71.4%	75.3%	75.6%	62.4%	68%	70.4%	77%
Established CVD							
CHF	26.2%	26%	29%	35.8%	31.1%	32%	32.3%
CHD	50.9%	52.2%	51.8%	–	54.4%	50.4%	51.6%
Angina	–	–	–	–	43.2%	32.8%	28.6%
MI	50.1%	49.4%	43.6%	–	–	–	–
Stroke	15.8%	16.6%	15.1%	15.7%	14.7%	18.4%	17.3%
CKD							
Mild	9.7%	10.7%	14.6%	11.7%	10.4%	10.8%	12.9%
Moderate-to-severe	30.1%	29.1%	29.5%	31%	29.5%	29.1%	33.1%
Arthritis	61.1%	59.8%	64.8%	53.2%	53.6%	55.3%	59%

(Continues)

TABLE 1 (Continued)

	Stroke			
	NHANES study period			
Characteristic	1988–1994	1999–2004	2005–2010	2011–2016
Sample *n* (weighted *N*)	644 (3,816,172)	606 (5,174,391)	678 (6,235,528)	640 (6,460,668)
Age, yrs				
≤ 39	5.3%	7.7%	5%	5.5%
40–59	21%	25.6%	27.4%	26.2%
≥ 60	73.7%	66.7%	67.6%	68.3%
Female	50.3%	57.9%	57.8%	54.2%
Race/ethnicity				
NH White	79.1%	73.2%	74%	66.5%
NH Black	12.8%	14.5%	15%	15.1%
Mexican American	2.2%	3.6%	4%	5.6%
Other	5.9%	8.7%	7%	12.8%
Comorbidities				
Diabetes	25.1%	22.2%	30.1%	30.3%
Hypertension	67.9%	75.3%	76.2%	77.5%
Established CVD				
CHF	20.2%	16.8%	17.1%	18.8%
CHD	–	19%	17.6%	18.8%
Angina	–	18.8%	12.4%	11.7%
MI	25.9%	20.5%	21.1%	20.2%
Stroke	–	–	–	–
CKD				
Mild	17%	13.1%	12.7%	12%
Moderate-to-severe	30.9%	33.5%	35.6%	33.3%
Arthritis	47.9%	55.9%	59.5%	51.3%

Abbreviations: CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; CVD = cardiovascular disease; MI = myocardial infarction; NH = non-Hispanic.

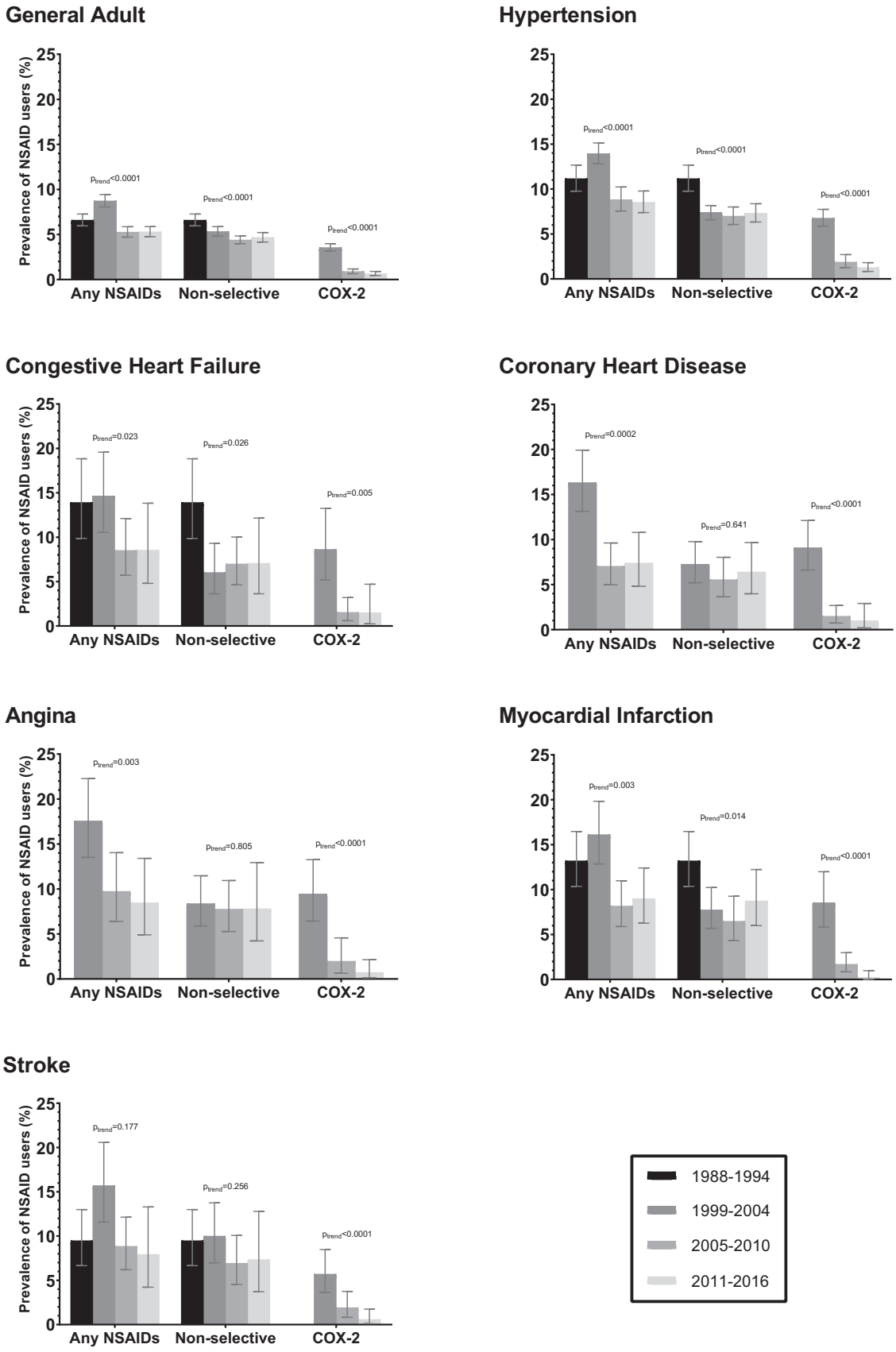

FIGURE 1 Weighted prevalence estimates of overall prescription NSAIDs, nonselective NSAIDs, and COX-2-selective inhibitors from 1988–2016 within each study cohort. Error bars indicate 95% confidence interval of the estimates. NSAIDs, nonsteroidal antiinflammatory drugs.

TABLE 2 Predictors of NSAID use by CVD Status Among Adults From 1999–2016

	Overall NSAIDs	Non-selective NSAIDs	COX-2-selective
	aOR (95% CI)[a]	aOR (95% CI)[a]	aOR (95% CI)[a]
HTN[b]	1.27 (1.13, 1.42)*	1.26 (1.09, 1.45)*	1.19 (0.97, 1.46)
CHF[b]	0.73 (0.56, 0.96)*	0.70 (0.50, 0.97)*	0.83 (0.51, 1.36)
CHD[b]	0.94 (0.74, 1.19)	0.84 (0.63, 1.12)	1.14 (0.76, 1.71)
Angina[b]	1.01 (0.77, 1.32)	0.95 (0.69, 1.29)	1.13 (0.72, 1.76)
MI[b]	0.95 (0.74, 1.23)	1.05 (0.78, 1.40)	0.81 (0.53, 1.24)
Stroke[b]	0.83 (0.63, 1.08)	0.96 (0.71, 1.28)	0.60 (0.39, 0.92)*

Abbreviations: aOR = adjusted odds ratio; CI = confidence interval; CHD = coronary heart disease; CHF = congestive heart failure; CVD = cardiovascular disease; HTN = hypertension; MI = myocardial infarction; NSAID = nonsteroidal antiinflammatory drug.

[a]Adjusted for age, sex, race/ethnicity, body mass index, self-reported health status, smoking status, self-reported comorbidities (chronic obstructive pulmonary disease [COPD] and arthritis), and chronic kidney disease (full model results available in the Supporting Information).

[b]Reference was patients without the respective CVD.

*$p < 0.05$.

FDA to caution against their use in patients with CVD. However, whether these changes have influenced the use of prescription NSAIDs among specific CVD populations is not well understood. Accordingly, we used a nationally representative sample of noninstitutionalized American adults to assess temporal trends in prescription NSAIDS within six CVD cohorts – hypertension, CHF, CHD, angina, MI, and stroke. Notably, we showed that overall trends in prescription NSAID use among all CVD populations declined, most significantly in the late 2000s, and primarily because of substantially reduced use of COX-2-selective inhibitors. To our knowledge, this is the first study to assess the long-term trends of NSAID use within specific CVD populations in the United States.

The results of our study indicate a decreasing trend in the use of prescription NSAIDs among patients with CVD, with a considerable decline in use comparing the 1999–2004 to 2005–2010 examination periods. This sharp decline was driven by a reduction in COX-2-selective inhibitor use during this time period, coinciding with the withdrawal of two COX-2-selective inhibitors, rofecoxib and valdecoxib, from the U.S. market, and well-publicized concerns regarding potential increased risk of adverse cardiovascular events with COX-2-selective inhibitors, more generally. A previous study using claims data found a similar decline in the prescriptions for COX-2-selective inhibitors within the general population.[13] The investigators also noted an increase in the prescriptions for nonselective NSAIDs after withdrawal of rofecoxib and valdecoxib. Conversely, we found consistent use of prescription nonselective NSAIDs over time, with similar trends observed in both CVD cohorts and the general adult population. Our results may be reflective of a more cautious approach to prescribing NSAIDs among both the general adult and CVD populations, given the increasing evidence underscoring the harmful cardiovascular effects of NSAIDs.[3,6,14]

Despite a declining trend overall, it is noteworthy that prescription NSAIDs continue to be used among a subset of these CVD populations. Our results indicate that prescription NSAID users represent roughly half a million U.S. adults within the high-risk CVD populations (i.e., CHF, CHD, angina, MI, and stroke). Previous studies also have noted regular use of NSAIDs among patients with CVD.[9–11] A study performed in the United Kingdom found consistent prescribing patterns of NSAIDs in patients with CVD from 2002 to 2010.[11] Another study using administrative claims databases from 2012 to 2016 observed a median NSAID prescribing rate of 11% among patients with hypertension, CHF, or CKD.[9] Our study adds to the current understanding of NSAID use within the CVD population by examining 30-year trends within specific CVD populations, namely those in which NSAIDs are advised to be avoided. We found that prevalence of prescription NSAIDs was similar across the different CVD cohorts (Figure S1), suggesting use remains prevalent regardless of the CVD subtype and even in those at highest risk of cardiovascular events.

We found notable associations between CVD status and prescription NSAID use. As expected, patients with CHF were less likely to be using any prescription NSAIDs and nonselective NSAIDs. Similarly, patients with stroke were less likely to be using prescription COX-2 selective inhibitors. These results may reflect clinician awareness of the potential cardiovascular effects of NSAIDs in patients with established CVD, and, accordingly, limiting their use within this high-risk population. Interestingly, we observed an increased likelihood of prescription NSAID use among patients with hypertension. In general, patients with any CVD likely represent a sicker population than the general public and thus have a higher probability of being treated with most drugs, including NSAIDs. However, a possible explanation for our observation of increased prescription NSAID use in those with hypertension, but decreased use in some other CVD states, is that clinicians may perceive a lower risk among patients with hypertension compared with those with established CVD, and, therefore, may be less inclined to avoid NSAID use in those with hypertension. Previous studies have underscored the BP-increasing effects and cardiovascular safety of NSAIDs within the hypertensive population[1,15,16]; however, little is currently known regarding the optimal risk/benefit ratio of prescribing NSAIDs in this population. Understanding the optimal risk/benefit ratio may assist clinicians to make more informed decisions regarding whether there are specific patients with hypertension in whom the benefits of NSAID use outweigh the risk of a cardiovascular event, particularly if use is limited to short-term.

A major strength of this study is the use of a nationally representative survey of the U.S. population over multiple examination periods spanning nearly 30 years. NHANES includes detailed measurements of self-reported and clinical information, allowing for determination of hypertension status using both self-reported questionnaires and clinical thresholds of elevated BP. Another strength of this study is the analysis of long-term trends in prescription NSAID use among six

CVD subtypes. We were able to focus our investigation within individual CVD subtypes by combining multiple examination periods, and thus, improving the statistical reliability of the estimates. Nonetheless, this study also has noteworthy limitations. First, the NHANES examination periods that were included in this study do not provide data on OTC medication use; therefore, our results are only representative of prescription NSAID use. Based on a previous cross-sectional report, overall prevalence of NSAID use within this population is likely considerably higher.[10] Second, because we combined examination periods into 6-year increments, our results may obscure trends in prescribing data. However, sensitivity analyses using 2-year examination periods indicated similar patterns of NSAID use (Tables S3 and S4). Third, self-reported information was used to define most of the CVD cohorts, creating the potential for misclassification of individuals (i.e., failure to identify some patients with CVD as such).

5 | CONCLUSIONS

The current study provides generalized estimates of prescription NSAID use among patients with CVD in the United States from 1988 to 2016. Importantly, our study underscores the routine use of prescription NSAIDs in a subset of the CVD population, despite a significant reduction in the mid-to-late 2000s primarily stemming from reduced use of COX-2-selective inhibitors. Additionally, patients with hypertension appeared to be more likely to be prescribed an NSAID compared with patients with other CVDs, possibly due to a perception of lower NSAID-attributable cardiovascular risk in this group. Our results suggest that increased efforts may be necessary to minimize the use of prescription NSAIDs, and encourage alternative options where feasible, among patients with CVD.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ORCID

Andrew Y. Hwang https://orcid.org/0000-0002-9766-7711
Steven M. Smith https://orcid.org/0000-0002-0201-839X

REFERENCES

1. Bavry AA, Khaliq A, Gong Y, Handberg EM, Cooper-Dehoff RM, Pepine CJ. Harmful effects of NSAIDs among patients with hypertension and coronary artery disease. *Am J Med*. 2011;124(7):614–620.
2. Varga Z, Sabzwari SRA, Vargova V. Cardiovascular risk of nonsteroidal anti-inflammatory drugs: an under-recognized public health issue. *Cureus*. 2017;9(4):e1144.
3. Kang DO, An H, Park GU, et al. Cardiovascular and bleeding risks associated with nonsteroidal anti-inflammatory drugs after myocardial infarction. *J Am Coll Cardiol*. 2020;76:518–529.
4. Pirlamarla P, Bond RM. FDA labeling of NSAIDs: review of nonsteroidal anti-inflammatory drugs in cardiovascular disease. *Trends Cardiovasc Med*. 2016;26(8):675–680.
5. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71(6):e13–e115.
6. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128(16):e240–e327.
7. Davis JS, Lee HY, Kim J, et al. Use of non-steroidal anti-inflammatory drugs in US adults: changes over time and by demographic. *Open Heart*. 2017;4(1):e000550.
8. Zhou Y, Boudreau DM, Freedman AN. Trends in the use of aspirin and nonsteroidal anti-inflammatory drugs in the general U.S. population. *Pharmacoepidemiol Drug Saf*. 2014;23(1):43–50.
9. Bouck Z, Mecredy GC, Ivers NM, et al. Frequency and associations of prescription nonsteroidal anti-inflammatory drug use among patients with a musculoskeletal disorder and hypertension, heart failure, or chronic kidney disease. *JAMA Intern Med*. 2018;178(11):1516–1525.
10. Castelli G, Petrone A, Xiang J, Shrader C, King D. Rates of nonsteroidal anti-inflammatory drug use in patients with established cardiovascular disease: a retrospective, cross-sectional study from NHANES 2009–2010. *Am J Cardiovasc Drugs*. 2017;17(3):243–249.
11. Chen Y, Bedson J, Hayward RA, Jordan KP. Trends in prescribing of non-steroidal anti-inflammatory drugs in patients with cardiovascular disease: influence of national guidelines in UK primary care. *Fam Pract*. 2018;35(4):426–432.
12. Chen TC, Clark J, Riddles MK, Mohadjer LK, Fakhouri THI. National health and nutrition examination survey, 2015–2018: sample design and estimation procedures. National Center for Health Statistics. *Vital Health Stat*. 2020;2(184):1–26.
13. Sun SX, Lee KY, Bertram CT, Goldstein JL. Withdrawal of COX-2 selective inhibitors rofecoxib and valdecoxib: impact on NSAID and gastroprotective drug prescribing and utilization. *Curr Med Res Opin*. 2007;23(8):1859–1866.
14. Danelich IM, Wright SS, Lose JM, Tefft BJ, Cicci JD, Reed BN. Safety of nonsteroidal antiinflammatory drugs in patients with cardiovascular disease. *Pharmacotherapy*. 2015;35(5):520–535.
15. Aljadhey H, Tu W, Hansen RA, Blalock SJ, Brater DC, Murray MD. Comparative effects of non-steroidal anti-inflammatory drugs (NSAIDs) on blood pressure in patients with hypertension. *BMC Cardiovasc Disord*. 2012;12:93.
16. Dong YH, Chang CH, Wu LC, Hwang JS, Toh S. Comparative cardiovascular safety of nonsteroidal anti-inflammatory drugs in patients with hypertension: a population-based cohort study. *Br J Clin Pharmacol*. 2018;84(5):1045–1056.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Hwang AY, Smith SM. U.S. trends in prescription nonsteroidal anti-inflammatory drug use among patients with cardiovascular disease, 1988–2016. *Pharmacotherapy*. 2021;41:247–256. https://doi.org/10.1002/phar.2488