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ORIGINAL RESEARCH

Identifying Risk Factors for Cardiovascular Events Among Active-Duty Service Members and Veterans Prescribed Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

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Background: Oral NSAIDs are widely used analgesic medications for the treatment of musculoskeletal and inflammatory conditions. NSAIDs are associated with adverse effects that arise from COX enzyme inhibition including cardiovascular events. The combined role of patient and prescription factors associated with NSAID use on cardiovascular risk is not well characterized.

Objective: The purpose of this study is to identify the risk factors with cardiovascular events among NSAID users.

Methods: This study is a retrospective, nested case–control study, within the DAVINCI database, among active-duty service members and veterans with at least one NSAID pharmacy claim between fiscal year (FY) 2015-FY2020. Inclusion criteria individuals ≥18 years of age received a prescription NSAID for ≥7-day supply and a duration ≥1 month overall. Cases experienced nonfatal myocardial infarction, nonfatal stroke, or new onset heart failure. Ten controls were selected per case. Risk factors were identified through logistic regression modeling.

Results: The risk factors with strongest association to the primary outcome included age starting at 45 up to 75 and older, the first 90 days of NSAID exposure, cerebrovascular disease, cardiomyopathy, and history of myocardial infarction. Cox-selectivity and dose did not appear to be clinically significant in their association with cardiovascular events.

Conclusion: The results of this study indicate that age, initial NSAID exposure, and comorbidities are more predictive than NSAID-specific factors such as COX-selectivity and dose. The results provide the framework for development of a risk score to improve prediction of NSAID-associated cardiovascular events.

Keywords: NSAID, cardiovascular, myocardial infarction, stroke, heart failure

Introduction

Oral nonsteroidal anti-inflammatory drugs (NSAIDs) have been the cornerstone of treatment for arthritis and inflammatory conditions for over a hundred years, making them one of the most utilized classes of medications worldwide.[1] NSAIDs are associated with significant adverse effects characterized primarily by gastrointestinal (GI) ulceration/bleeding and cardiovascular events, including myocardial infarction and cerebrovascular disease.[2] While the risk of GI ulceration/bleeding is well studied with mitigation and prevention strategies available, there remains a dearth of evidence to assess NSAID-related risk prior to a cardiovascular event and guide clinical recommendations for prevention and mitigation strategies.[3–7] Studies evaluating NSAID-related cardiovascular risk have focused on COX selectivity, dose-dependent effects, and duration of NSAID therapy with variable and often conflicting results.[8–13]

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Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality worldwide, accounting for nearly 17.9 million deaths annually, representing 31% of all global deaths. CVD encompasses conditions such as myocardial infarction, stroke, and heart failure. Numerous studies have highlighted the prevalence of CVD and its associated risk factors.[14] Well-established risk factors for cardiovascular disease include hypertension, dyslipidemia, smoking, obesity, diabetes mellitus, sedentary lifestyle, and family history of CVD.[15] Several guidelines recommend avoidance of NSAIDs due to their potential adverse effects.[16–19] However, NSAIDs remain first-line medications for many common pain conditions, making avoidance impractical without clear guidance regarding the magnitude of the risk factors most strongly associated with cardiovascular events.[20–29] Furthermore, NSAIDs are critical non-opioid pharmacotherapy options serving as reasonable alternatives to opioid therapy for many chronic pain conditions in the midst of the opioid overdose crisis.[30,31]

This study is a collaboration between clinicians from the Veterans Health Administration (VHA) and the health science outcomes research group from the Department of Defense (DoD). This study aims to investigate the impact of demographics, comorbidities, and NSAID-specific risk factors on cardiovascular outcomes associated with NSAID use. Through this collaboration, we leverage the comprehensive databases of both the VA/DoD, which represents a more demographically diverse cohort and improves generalizability of outcomes. This study lays the groundwork for development of a risk index to improve predictability of cardiovascular events associated with NSAID use.

Methods

Study Design and Data Source

A retrospective case control leveraging the DAVINCI (Data Analysis and Visualization Initiative) data was used to identify the factors associated with cardiovascular events among patients who received an NSAID. DAVINCI is a collaborative effort between the Department of Defense (DoD) and the Veterans Health Administration (VHA) within the Department of Veterans Affairs (VA) in the US.[32] The DAVINCI database integrates and analyzes various types of health data, including electronic health records (EHRs), administrative data, and clinical data from both the DoD and the VA using Observational Medical Outcomes Partnership (OMOP) common data models. More specifically, the clinical records include information regarding healthcare visits, conditions, dispensed drugs, and procedures in both the inpatient and outpatient settings. By combining these datasets, researchers and healthcare providers can gain a more comprehensive understanding of the health outcomes and healthcare utilization of military personnel, veterans, and their families, examine the long-term effects of military service, and evaluate the effectiveness of different interventions and treatments.

Study Cohort

Individuals with at least one NSAID pharmacy claim with a days' supply greater than 7 days between October 1, 2016 and September 30, 2020 were identified in the DAVINCI national administrative healthcare database. The authors determined that requiring a days' supply greater than 7 days effectively removed many short-term prescriptions from being associated with distant CV events while recognizing that previous studies indicated that CV risk may be significant within the first 30 days.[6,11,33] NSAIDs were identified by national drug codes. Individuals under the age of 18, with missing sex, or missing race variables were excluded.

Matching and Index Date Assignment

The first occurrence of a cardiovascular event was the primary outcome of interest. A cardiovascular event included a non-fatal myocardial infarction, non-fatal stroke, and new onset of heart failure and was defined using the International Classification of Disease, 10th Revision, Clinical Modification (ICD10-CM) codes listed in Supplementary Table 1. All-cause mortality data was not included because it was not specific to cardiovascular disease and confounding could not be controlled. Cases were defined as individuals with at least one NSAID pharmacy claim with a days' supply greater than 7 days during the study period and a subsequent claim for a cardiovascular event. The date of the first identified event for a cardiovascular event following a qualifying NSAID pharmacy prescription during the study period served as the index date. Controls were defined as individuals with at least one NSAID pharmacy claim with a days' supply greater than 7

days during the study period and no subsequent claim for a cardiovascular event during the study period. For each case, 10 control patients were randomly assigned. The index date of the case was assigned to each of the 10 control patients it was matched to. To ensure that included individuals were regular users of TRICARE or VHA health services, individuals were required to have a recorded encounter in the 180 to 365 days prior to their identified or assigned index date.

Covariates

Baseline demographic variables were collected in the 180 days prior to the index date. These variables included age, sex, and race. Baseline comorbidity and prescription use measures were selected based on their known association with the receipt of an NSAID and/or the outcome. Comorbidity measures included diabetes,[15] hypertension,[15] dyslipidemia,[15] history of myocardial infarctions,[14] arthritis or spondylitis,[34] peripheral artery disease,[15] chronic kidney disease,[14] atherothrombotic disease,[14] history of tobacco use,[15] cerebrovascular disease,[15] coronary artery disease,[15] cardiomyopathy,[14] obstructive sleep apnea (OSA),[14] liver dysfunction,[14] and chronic obstructive pulmonary disease (COPD).[14] Prescription use measures included the use of aspirin and other anticoagulants. NSAID-specific drug information included was active ingredient, selectivity[9,10,35,36] (Cox 1, Cox 2, and non-selective), dosage[10,13,33,35] (low/medium and high dose), and time since initial exposure[6,13,33,35] (≤30, 31–90, 91–180, 181–365, 366–730, 731+, and no exposure) (see Supplementary Table 1 for ICD-10 codes used for all predefined risk factors).

Statistical Analyses

Descriptive and bivariate analyses were conducted using means, medians, interquartile range, and frequencies. Chi-squared tests were conducted for categorical variables, and t-tests were conducted for continuous variables to compare the characteristics among the identified cases and controls. Conditional multivariable logistic regression was used to calculate to explore the role of factors potentially associated with a cardiovascular event. All baseline demographic, comorbidity, prescription use, and NSAID-specific drug information covariates were included in the regression model. Odds ratios (ORs), 95% confidence intervals (CIs), and p-values were calculated to evaluate the presence and strength of the associations between the covariates and the primary composite outcome. Subgroup analyses evaluated the role of covariates on the risk of the individual conditions (non-fatal myocardial infarction, non-fatal stroke, and new onset heart failure) that make up the composite primary outcome. Additionally, the primary model was run combining active ingredient and dose as a factor in the model. A 5% significance level was used for all analyses. Model discrimination was assessed using the c-statistic, area under the curve (AUC), and receiver operating characteristic curve (ROC) measure.[37] All analyses were conducted on a patient level. All statistical analyses were performed using R. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[38] This study was determined to be exempt by the Defense Health Agency Institutional Review Board.

Results

We identified 237,852 patients with a claim of a cardiovascular event (myocardial infarction, non-fatal cerebrovascular accident, or new heart failure) during the study period. During the study period, 231,967 patients had a pharmacy claim for an NSAID and encounter data for at least 6 months prior to the cardiovascular event (index date). Among those who received an NSAID prescription from VA/DoD during the study period, 2,319,670 patients without cardiovascular events who met selection criteria (see Figure 1) were assigned as controls.

Descriptive Analysis

Median age of cases was 69 and controls 49. As shown in Table 2, cases were more likely than controls to be older, black or other than white race, or male sex.

Compared with controls, patients with cardiovascular events were more likely to have high disease burdens. As shown in Table 1, cases had significantly higher frequency of diagnosed conditions including diabetes, hypertension, dyslipidemia, arthritis, peripheral artery disease, chronic kidney disease, atherothrombotic disease, history of tobacco use, coronary artery disease, cardiomyopathy, obstructive sleep apnea, chronic obstructive pulmonary disease (COPD), and

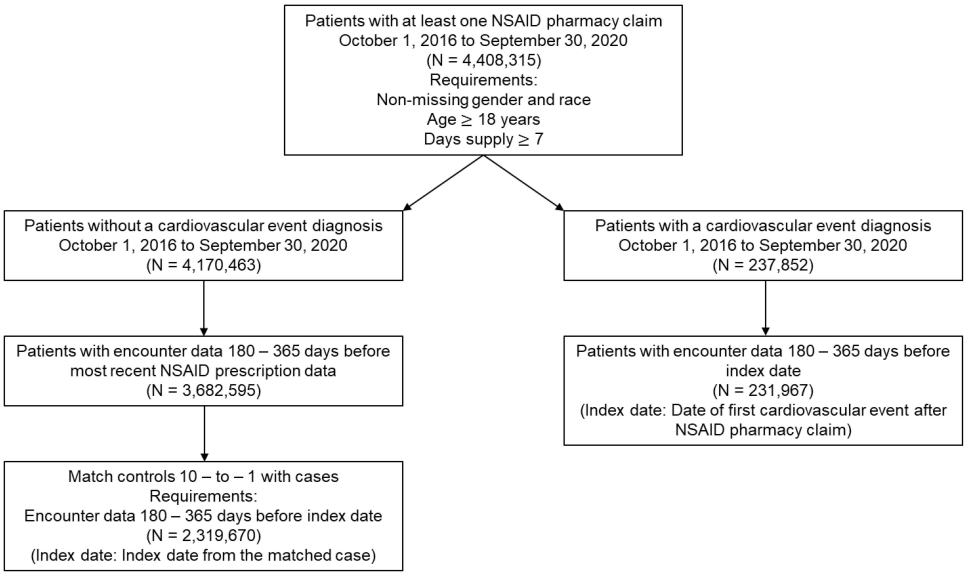

Figure 1 Consort diagram.

liver dysfunction. In addition to disease comorbidity, cases also reported higher frequency of previous cardiovascular events specifically history of myocardial infarction and cerebrovascular accident.

VA/DoD prescription data indicated a higher percentage of cases receiving aspirin and anticoagulants compared to controls. COX-2 and non-selective NSAIDs were prescribed more often in cases, but COX-1 selective NSAIDs were prescribed more often in controls driven by ibuprofen which was prescribed more frequently in controls. All other individual NSAIDs were prescribed more frequently in cases including celecoxib, diclofenac, etodolac, indomethacin, meloxicam, naproxen, piroxicam, sulindac, and several others with low prescription counts for both cases and controls. NSAIDs were prescribed more frequently across low/medium and high doses tracked.

Multivariable Analysis

The logistic regression model for the dichotomous outcome of NSAID-related composite cardiovascular event or myocardial infarction, nonfatal cerebrovascular accident, and new heart failure resulted in multiple, independent, statistically significant associations. History of heart failure was removed from the composite outcome as there were

Table 1 Diagnostic Codes for Cardiovascular Events and Predefined Risk Factors

ICD-10-CM Diagnosis Codes	Description
Cardiovascular events	
Non-fatal myocardial infarction	
I21	Acute myocardial infarction
I22	Subsequent ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction
I25.6	Silent myocardial ischemia
I46	Cardiac arrest
Non-fatal stroke	
I63	Cerebral infarction
New onset heart failure	
I50	Heart failure

Abbreviations: ICD-10-CM, International Classification of Disease, 10th Revision, Clinical Modification; STEMI, ST elevated myocardial infarction; NSTEMI, non-ST elevated myocardial infarction.

Table 2 Baseline Demographics & Predefined Risk Factors

Characteristics	Cases (n = 231,967)		Controls (n = 2,319,670)		P value
	n (%)		n (%)		
DEMOGRAPHICS					
Age (years), median (IQR)	69	14	49	32	<0.001
Age Group (years)					<0.001
18–34	3971	1.71	673,864	29	
35–44	6444	2.78	346,182	14.9	
45–54	18,485	7.97	334,967	14.4	
55–64	54,305	23.4	404,898	17.5	
65–74	89,380	38.5	414,475	17.9	
75+	59,382	25.6	145,284	6.26	
Male	216,417	93.3	1,916,362	82.6	<0.001
Race					<0.001
Black or African American	47,039	20.3	5,000,047	21.6	
White	145,523	62.7	1,553,051	67	
Other	39,405	17	266,572	11.5	
PREDEFINED RISK FACTORS					
Diabetes	96,042	41.4	359,266	15.5	<0.001
Hypertension	181,387	78.2	829,599	35.8	<0.001
Dyslipidemia	148,788	64.1	773,176	33.3	<0.001
History of Myocardial Infarction	13,314	5.74	14,497	0.625	<0.001
Arthritis or Spondylitis	6887	2.96	31,240	1.35	<0.001
Peripheral Arterial Disease	21,595	9.31	38,968	1.68	<0.001
Chronic Kidney Disease	29,643	12.8	64,783	2.79	<0.001
Atherothrombotic Disease	10,885	4.69	20,250	0.873	<0.001
History of Tobacco Use (Dx Only)	34,515	14.9	190,430	8.21	<0.001
Cerebrovascular Disease	41,791	18	38,342	1.65	<0.001
Coronary Artery Disease	69,186	29.8	126,074	5.43	<0.001
Cardiomyopathy	16,127	6.95	17,439	0.752	<0.001
Aspirin Use	69,054	29.8	170,292	7.34	<0.001
Other Anticoagulant Use	38,386	16.5	52,462	2.26	<0.001
Obstructive Sleep Apnea	56,751	24.5	357,819	15.4	<0.001
Liver Dysfunction	7497	3.23	26,553	1.14	<0.001
COPD	50860	21.9	119,186	5.14	<0.001

(*Continued*)

Table 2 (Continued).

Characteristics	Cases (n = 231,967)		Controls (n = 2,319,670)		P value
	n (%)		n (%)		
PRESCRIPTION DRUG INFORMATION					
BY ACTIVE INGREDIENT					
Celecoxib	17,587	7.58	106,505	4.59	<0.001
Diclofenac	19,681	8.48	124,792	5.38	<0.001
Diflunisal	101	0.0435	369	0.0159	<0.001
Etodolac	6841	2.95	39,324	1.7	<0.001
Fenoprofen	80	0.0345	349	0.015	<0.001
Flurbiprofen	60	0.0259	230	0.00992	<0.001
Ibuprofen	69,068	29.8	815,442	35.2	<0.001
Indomethacin	10,302	4.44	49,567	2.14	<0.001
Ketoprofen	37	0.016	181	0.0078	<0.001
Ketorolac	198	0.0854	1181	0.0509	<0.001
Mefenamic Acid	3	0.0013	88	0.00379	0.08179
Meloxicam	62,405	26.9	392,807	16.9	<0.001
Nabumetone	1543	0.665	7784	0.336	<0.001
Naproxen	53,190	22.9	496,578	21.4	<0.001
Piroxicam	526	0.227	4170	0.18	<0.001
Sulindac	2451	1.06	11,862	0.511	<0.001
Other (Summation of Highlighted)	2540	1.09	14,312	0.617	<0.001
BY SELECTIVITY					
COX 1	82,151	35.4	878,473	37.9	<0.001
COX 2	86,072	37.1	532,371	23	<0.001
Non-Selective	71,888	31	614,930	26.5	<0.001
BY DOSE CATEGORY					
Low/Medium Dose	189,875	81.9	1,656,424	71.4	<0.001
High Dose	44,190	19.1	300,509	13	<0.001
TIME SINCE INITIAL EXPOSURE (DAYS)					<0.001
LEQ 30	15,630	6.74	136,896	5.9	
31–90	33,182	14.3	260,316	11.2	
91–180	38,287	16.5	319,594	13.8	
181–365	52,383	22.6	466,322	20.1	

(*Continued*)

Table 2 (Continued).

Characteristics	Cases (n = 231,967)		Controls (n = 2,319,670)		P value
	n (%)		n (%)		
366–730	54,133	23.3	459,522	19.8	
731+	32,563	14	257,109	11.1	
No Exposure	5789	2.5	419,911	18.1	

only 10 cases of prior heart failure despite the large sample size. The final model yielded a c-statistic of 0.88. As shown in Table 2, significant demographic predictors of NSAID-related cardiovascular events included all ages starting at 35–44 (OR = 2.59; CI 2.49–2.70), 45–54 (OR = 5.69; CI 5.49–5.89), 55–64 (OR = 9.72; CI 9.39–10.05), 65–74 (OR = 12.35; CI 11.94–12.79), and 75 and above (OR = 20.04; CI 19.35–20.77), black and racial groups other than white. Concomitant health conditions that were most strongly associated with the occurrence of NSAID-related cardiovascular events were cerebrovascular disease (OR = 5.04; CI 4.95–5.13), cardiomyopathy (OR = 2.70; CI 2.63–2.78), and history of myocardial infarction (OR 2.07; CI 2.01–2.13). Other comorbidities that were statistically significant in their association with the primary outcome included coronary artery disease, COPD, hypertension, atherothrombotic disease, chronic kidney disease, hepatic dysfunction, history of tobacco use, diabetes, peripheral arterial disease, and obstructive sleep apnea (see Table 3).

Prescriptions for anticoagulants (OR = 2.58; CI 2.53–2.62) and aspirin (OR = 1.71; CI 1.69–1.73) significantly increased risk of NSAID-related CV events. As shown in Table 2, COX-1 selectivity (OR = 1.03; CI 1.00–1.05), and high dose NSAID use (OR = 1.02; CI 0.98–1.05) were not statistically significant but COX-2 (OR = 1.09; CI 1.06–1.11), non-selective (OR = 1.08; CI 1.05–1.10), and low/medium dose (OR = 1.06; CI 1.02–1.10) were statistically significant but with minimal impact on effect size. Time since initial exposure to NSAIDs is significant across all time intervals but appears to be high initially (OR = 8.97; CI 8.58–9.37) and peaks between 30 and 90 days (OR = 9.54; CI 9.15–9.96) before slowly tapering off the longer they are exposed to NSAIDs. Full regression results, including secondary outcomes

Table 3 Primary Outcome: Composite Cardiovascular Events

Covariates	All Patients (Cases, n = 231,967; Controls, n = 2,319,670)			
	Odds Ratio	95% CI		P value
DEMOGRAPHICS				
Age Group (years)				
18–34 (reference)				
35–44	2.59	2.49	2.70	<0.001
45–54	5.69	5.49	5.89	<0.001
55–64	9.72	9.39	10.05	<0.001
65–74	12.35	11.94	12.79	<0.001
75+	20.04	19.35	20.77	<0.001
Male	1.18	1.16	1.20	<0.001

(*Continued*)

Table 3 (Continued).

Covariates	All Patients (Cases, n = 231,967; Controls, n = 2,319,670)			
	Odds Ratio	95% CI		P value
Race				
Black or African American	1.08	1.07	1.10	<0.001
Other	1.13	1.12	1.15	<0.001
White (reference)				
PREDEFINED RISK FACTORS				
Diabetes	1.33	1.32	1.35	<0.001
Hypertension	1.57	1.55	1.59	<0.001
Dyslipidemia	0.91	0.90	0.92	<0.001
History of Myocardial Infarction	2.07	2.01	2.13	<0.001
Arthritis or Spondylitis	1.22	1.19	1.26	<0.001
Peripheral Arterial Disease	1.23	1.21	1.26	<0.001
Chronic Kidney Disease	1.42	1.39	1.44	<0.001
Atherothrombotic Disease	1.55	1.51	1.60	<0.001
History of Tobacco Use (Dx Only)	1.37	1.35	1.39	<0.001
Cerebrovascular Disease	5.04	4.95	5.13	<0.001
Coronary Artery Disease	1.77	1.75	1.80	<0.001
Cardiomyopathy	2.70	2.63	2.78	<0.001
Aspirin Use	1.71	1.69	1.73	<0.001
Other Anticoagulant Use	2.58	2.53	2.62	<0.001
Obstructive Sleep Apnea	1.06	1.05	1.07	<0.001
Liver Dysfunction	1.40	1.36	1.44	<0.001
COPD	1.61	1.59	1.63	<0.001
PRESCRIPTION DRUG INFORMATION				
BY SELECTIVITY				
COX 1	1.03	1.00	1.05	0.0291
COX 2	1.09	1.06	1.11	<0.001
Non-Selective	1.08	1.05	1.10	<0.001
BY DOSE CATEGORY				
Low/Medium Dose	1.06	1.02	1.10	0.0014
High Dose	1.02	0.98	1.05	0.3619
TIME SINCE INITIAL EXPOSURE (DAYS)				

(*Continued*)

Table 3 (Continued).

Covariates	All Patients (Cases, n = 231,967; Controls, n = 2,319,670)			
	Odds Ratio	95% CI		P value
No Exposure (reference)				
LEQ 30	8.97	8.58	9.37	<0.001
31–90	9.54	9.15	9.96	<0.001
91–180	8.69	8.33	9.07	<0.001
181–365	8.02	7.69	8.37	<0.001
366–730	7.14	6.85	7.45	<0.001
731+	5.80	5.55	6.06	<0.001

and factors that were not statistically significant in relation to the outcome in the logistic regression model, are provided in the Supplementary Table 2–5.

Discussion

Our study reaffirms the association between NSAID use and an increased risk of cardiovascular events producing a robust multivariable model that characterized the risk of NSAID-related myocardial infarction, nonfatal stroke, and new heart failure in a composite outcome of cardiovascular events. Age, NSAID exposure within the past 90 days, and history of myocardial infarction or cerebrovascular disease were the factors most strongly associated with a cardiovascular event in the NSAID-exposed cohort of predominantly US Veterans and active-duty military personnel.

Consistent with published findings on cardiovascular risk, we found certain demographic characteristics, and comorbid conditions were factors associated with NSAID-related cardiovascular events. Demographic variables previously identified as risk factors and confirmed in the present study, which include black and other non-white racial groups.[14] Comorbidities previously identified as risk factors and confirmed in the present study, included history of myocardial infarction, cerebrovascular disease, coronary artery disease, and atherothrombotic disease.[4,6,8,9]

Cardiovascular disease increases with age and comorbidities.[39,40] However, there is a paucity of research evaluating the cardiovascular risk of an aging population using NSAIDs for common pain conditions. The odds ratio for experiencing a cardiovascular event doubles starting at 45 years-old and increases steadily each decade until at 75 years-old and beyond the risk has nearly quadrupled. This underpins the urgent need for clinicians to consider age not just as a chronological measure but as a marker of the cumulative effect of various physiological changes and disease states that predispose older individuals to cardiovascular risks and who may have attenuated compensatory mechanisms to deal with the cardiovascular strain NSAIDs may impose. In clinical decision-making, this calls for a paradigm shift from a one-size-fits-all to a more age-attuned prescription model. Practitioners should also be mindful of the comorbidities that significantly elevate cardiovascular risk when NSAIDs are used, as identified in the study. This suggests that medical practitioners should employ a conservative approach when initiating NSAID therapy in the elderly, perhaps opting for the lowest effective doses and considering alternative pain management strategies where feasible. In addition, these data support the need for regular cardiovascular monitoring of patients on NSAIDs, particularly in the early stages of treatment.

In our study, we have identified several critical aspects that both align with and diverge from the current body of literature on the cardiovascular risks associated with NSAID use. Previously published studies evaluating NSAID-related cardiovascular risk focused on three aspects of NSAIDs including COX-1 vs COX-2 selectivity,[4,6,9,10,12,13,33–36,41,42] dose-dependent risks,[4,6,9,11–13,33,41] and length of NSAID exposure.[6,11,13,33,35] The present study confirms previously

published reports on increased risk with early exposure to NSAIDs with the highest risk being the first 90 days of treatment after which the risk gradually diminishes but remains significantly higher than most other risk factors reviewed. In contrast to previous studies that were highly focused on evaluating the impact of COX selectivity on cardiovascular risk, the present study characterizes these effects as minor even when statistically significant. This raises questions about clinical significance when compared against other risk factors evaluated and potentially explains the heterogeneity of previously published results with inconsistent conclusions about the risk of individual NSAIDs. The dose-dependent risks of NSAIDs remain unclear as the low/moderate and high dose categories for each NSAID were not statistically significant for most outcomes despite the large cohort. The low/moderate dose category was significant for the primary outcome but not MI or non-fatal stroke and the odds ratio 1.03 is not clinically significant compared to other risk factors. These findings offer a comprehensive blend of reinforcement of established data and fresh insights, contributing to a more nuanced understanding of NSAID-related cardiovascular events.

The large dataset resulted in meaningful comparisons of each secondary outcome with most predefined risk factors achieving statistically significant results. Myocardial infarction is the most studied NSAID-related cardiovascular outcome.[4,6,8,11,13,33,35,39] In the present study, the comorbidities serving as predefined risk factors most strongly associated with a myocardial infarction were history of myocardial infarction, coronary artery disease, and cardiomyopathy. Stroke is often evaluated as a vascular event or hemorrhagic stroke; however, non-fatal stroke was chosen in the present study due to NSAIDs dual mechanism potentially resulting in both hemorrhagic and thromboembolic events.[4,6,8,40] For non-fatal stroke, the comorbidities that were the strongest risk factors were cerebrovascular disease, atherothrombotic disease, and hypertension. New heart failure is the least studied of the secondary outcomes, but the current study confirms previous published reports on NSAID-related risks.[4,36] All secondary outcomes were influenced by age, but heart failure was the most influenced at every age group evaluated. The comorbidities with the strongest association to new heart failure were cardiomyopathy, coronary artery disease, and chronic obstructive pulmonary disease (COPD) (see Supplementary Tables S2-S5). Our findings corroborate the literature's emphasis on the role of comorbid conditions, such as hypertension, diabetes, and atherothrombotic disease, in amplifying cardiovascular risks in NSAID users. This underscores the importance of considering underlying health conditions in prescribing practices.

The use of aspirin and anticoagulants were among the highest odds ratios for predefined risk factors for both primary and secondary outcomes. Due to their ability to minimize risk of thromboembolic events, it is unlikely that their mechanism contributed to events other than non-fatal stroke. However, patients with significant underlying risk or previous cardiovascular events may be on these agents for secondary prevention, which may explain their strong association with future cardiovascular events.

Limitations

Our study provides critical insights into NSAID-related cardiovascular risks but also presents several limitations related to potential confounders and biases. Administrative data inherently carry risks of coding errors, misclassification, missing data or incomplete data, which could influence the accuracy of comorbidity profiles and medication adherence. The absence of detailed patient lifestyle behaviors, genetic predispositions, and socioeconomic factors from the database introduces potentially unknown confounding variables that are challenging to control. The over-the-counter (OTC) medication coverage is self-reported within VHA and DoD, and it is possible that patients obtained and utilized NSAIDs from unreported sources. Although the large dataset allowed for meaningful comparisons, the study was limited to a specific population of US Veterans and active-duty military personnel, which may affect the generalizability to other populations. These factors underscore the importance of a cautious approach when applying our findings to clinical practice and policy-making, especially in demographically diverse settings outside of the VA/DoD population.

Conclusion

The results of our study both reinforce and expand the existing body of knowledge regarding NSAID use and cardiovascular risk. It emphasizes the inherent risks of these medications and the exacerbating role of comorbidities and concomitant medication use. Our research offers new insights into the impact of specific demographic factors and the relative influence of NSAID-specific risk factors including age starting at 45 up to 75 and older, NSAID exposure within

the past 90 days, cerebrovascular disease, cardiomyopathy, and history of myocardial infarction are the factors most strongly associated with NSAID-related cardiovascular events. Cox-selectivity and dose did not appear to be clinically significant in their association with cardiovascular events. These findings underscore the critical importance of a personalized approach in prescribing NSAIDs, taking into account patient-specific factors such as age, race, and detailed comorbidity profiles to optimize cardiovascular safety among patients requiring NSAID therapy. These results also facilitate the creation of a risk index designed to predict cardiovascular events related to NSAID use and should be utilized in a prospective trial to validate results.

Disclosure

The authors report no conflicts of interest in this work.

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