NSAIDs Prescription Prevalence after a Cardiovascular Event Related Hospitalization in Medicaid Beneficiaries from Puerto Rico

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Objective: Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for pain and inflammation. NSAIDs are associated with serious adverse effects and cardiovascular (CV) risks that include myocardial infarction, stroke and heart failure. In the period of time immediately after a CV event, modification to the drug therapy regimen and lifestyle habits should be instituted to decrease morbidity and mortality. The objective of this study is to measure the prevalence of NSAIDs prescribing in the immediate 90 days after a CV-related hospitalization in Medicaid beneficiaries in Puerto Rico.

Methods: Hospitalization claims were used to identify beneficiaries with a CV-related hospitalization during the study period, and pharmacy claims were used to evaluate the occurrence of NSAIDs prescribing post-discharge.

Results: A total of 4,195 beneficiaries with at least one CV-related hospitalization were identified. Out of these beneficiaries, 774 (18.5%) had at least one pharmacy claim for an NSAID post discharge, and 401 (9.6%) had at least one pharmacy claim for an NSAID within 90 days post-discharge. The average time span between the discharge date and the first NSAID claim was 135 days.

Conclusion: Almost 20% of all beneficiaries who were hospitalized for a CV event received an NSAID during the study period, with 10% of patients receiving it during the immediate 90 days post-discharge. It represents a major challenge for our healthcare system, as it may reflect unawareness on the impact of proved evidence in clinical decision making. [*P R Health Sci J 2016;35:209-214*]

Key words: Non-steroidal anti-inflammatory drugs, NSAIDs, Cardiovascular events, Pharmacy Claims, Puerto Rico

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for pain management (1). Although being highly effective, current evidence indicates that NSAIDs are associated with an increased risk of cardiovascular (CV) events, including myocardial infarction (MI) and stroke (2-5). In 2005, a black box warning was issued by the FDA for all NSAIDs because of these risks (6). Expert recommendations and pertinent treatment guidelines for the management of pain and inflammatory diseases advise against the use of these drugs in patients with history of CV events or in those at high risk (7-9).

The mechanism of action of NSAIDs has been well studied. The efficacy and safety of this therapeutic group revolves around the inhibition of the cyclooxygenase (COX) enzyme. COX main function is the biosynthesis of prostaglandins, and exists as two isoenzymes: COX-1 and COX-2. COX-1 is constantly expressed in most body tissues, while COX-2 is primarily present at sites of inflammation (5). NSAIDs may be classified as non-selective, if they inhibit both COX-1 and COX-2, or selective, if they inhibit COX-2 isoenzyme at a much greater extent. Non-selective NSAIDs have been associated mainly with an increased risk of GI ulceration and some agents with an increased risk of CV events. Selective COX-2 inhibitors, such as celecoxib, have been primarily linked to an increased risk of CV events (2).

COX enzyme metabolizes arachidonic acid to the prostanoids prostacyclin (PGI_2) and thromboxane A_2 (TXA_2), which are important components in the maintenance of vascular homeostasis. While PGI_2 causes vasodilation and inhibits platelet aggregation, TXA_2 causes vasoconstriction and promotes platelet aggregation (10). PGI_2/TXA_2 balance in the vascular system is critical, and a normal production of

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PGI_2 is essential to control vessel tone and inhibit thrombosis. Irreversible inhibition of COX-1 by low doses of aspirin has been proven to rapidly inhibit the synthesis of PGI_2 and TXA_2, but, while the ability to synthetize PGI_2 is recovered rapidly afterward, TXA_2 synthesis is inhibited for a longer period of time. In the platelets the production of TXA_2 is solely COX-1 dependent and irreversible inhibition of COX-1 will result in inhibition of platelet aggregation for the platelet's lifecycle (11). This is the basis for the cardioprotective benefits of low dose aspirin in the prevention of thrombotic CV events (2,12).

Although normal endothelial and vascular cells express COX-1, COX-2 has been identified in proliferating vascular tissues, as in atherosclerosis (13). Inhibition of COX-2 results in a decrease of pro-inflammatory cells, but also in the suppression of PGI_2 synthesis, resulting in a PGI_2/TxA_2 imbalance that may explain the thrombotic CV risks associated with selective inhibitors (2,9). NSAIDs have also been linked to an increase in sodium and water retention that can worsen hypertension and exacerbate heart failure (HF) (7). Although CV adverse effects seem to be greater in patients at high risk or with a prior history of CV disease, healthy patients may also be at risk (3).

Not all currently available NSAIDs have been associated with an increased risk of CV events and the risk appears to differ among individual agents. The scientific data is less abundant for the relationship between NSAIDs and stroke; yet, a study showed that diclofenac is associated with an increased risk for this type of CV event (14). Many studies have demonstrated an increased risk of MI with the use of selective and non-selective NSAIDs, while naproxen's risk appears to be neutral (2,3,15,16).

Although the risks associated with NSAIDs in patients with established CV disease are well documented in the literature, recent studies have revealed a high incidence of NSAIDs' prescribing after an MI (36%-44% patients) (4,15,17,18). Mortality due to recurrent MI appears to be independent of treatment duration with an NSAID, and an increased risk has been documented at the initiation of therapy and persists afterward (4,15,18) Another study showed a similar pattern of NSAIDs prescribing in patients with HF, with 33.9% of patients having at least one claim during the study period (19).

According to the Puerto Rico Department of Health, CV diseases such as MI, HF, and stroke, were the leading causes of death in 2010. In 2011, the prevalence of coronary heart disease, MI, and stroke in Puerto Rico was 7.2%, 4.8%, and 1.7%, respectively (20). To our knowledge, no study has been published addressing the use of NSAIDs in patients with established CV disease, specifically MI, stroke, or HF, in the Puerto Rican population. The objective of this study is to measure the prevalence of NSAIDs prescribing in the immediate 90 days following a CV hospitalization due to HF, stroke, or MI among the Medicaid population in PR, who constituted 57.7% of the population during 2010 to 2011 (21). This investigation aims to provide a foundation to highlight the need for evidence based guidelines for the safe management of pain in patients with or at a high risk of CV diseases.

Methods

A two-year longitudinal study was designed to assess administrative claims submitted to the Puerto Rico Health Insurance Administration (PRHIA) between January 1, 2010 and September 30, 2011 to identify hospitalizations related to a primary diagnosis of HF, stroke or MI. A list of the International Statistical Classification of Diseases and Related Health Problems, 9th edition codes (ICD-9s) used to identify CV-events related hospitalization could be found in Appendix A (22). Pharmacy claims were used to capture NSAIDs prescribing post-discharge. A scrambled unique identifier was used to merge the hospitalizations and pharmacy related claims. Due to lower systemic absorption, formulations for topical, ophthalmic and otic administration were excluded from the study (23). Doses of aspirin 81mg and 325 mg were excluded due to cardioprotective properties (12,24). NSAIDs formulated as combination products (e.g. diclofenac/misoprostol, oxycodone/ibuprofen) were not included in the PRHIA formulary, and therefore were excluded.

The discharge date for the CV-related hospitalization was identified as the index date. Pharmacy claims in the study population for any NSAID prescription after the selected index date (discharge home date) were identified by a flag. Two types of flags were designed for this study: 1) Red-flags, for pharmacy claims for NSAIDs that occurred within 30 days after the index date, and 2) Yellow flags, for pharmacy claims for NSAIDs that occurred between 31- 90 days after the index date. The study period selected to identify NSAIDS prescriptions in patients with a discharge home claim related to a cardiovascular event between January 1, 2010 to September 30, 2011 was up to 3 months after the last index date identified in the selected period. A timeframe of 90 days seemed appropriate considering that primary care provider visits and prescription dispensing usually occur soon after an event.

A secondary analysis using beneficiaries instead of hospitalization claims as the unit of analysis was performed. In order to accomplish this task two rules were set: 1) For beneficiaries with more than one hospitalization claim during the study period, the one with the discharge date closest to the date of the first NSAID pharmacy claim was chosen; 2) For beneficiaries generating multiple pharmacy claims for NSAIDs, only the first generated claim after the index date was used to generate a yellow or red flag. The resulting group of beneficiaries was further subdivided into two categories: 1) Those receiving an NSAID claim within the first 30 days after the index date; 2) Those receiving an NSAID claim more than 30 days after the index date. Beneficiaries may have multiple hospital-claims for CV-related hospitalizations or pharmacy-claims for NSAID during the study period. Therefore, results will be presented at two levels: 1) using claims as the unit of analysis (claim-level); and using beneficiaries as the unit of analysis (beneficiary-level).

Descriptive statistics such as frequency count, percentages, averages and standard deviations were used to describe the

beneficiaries' socio-demographics and hospital related variables as well as hospitalization and pharmacy claims data. Statistical differences by age, gender, amount paid for hospitalization, and length of hospital stay between the groups of beneficiaries who received their first NSAID within 30 days after the index date, and those who received it more than 30 days after the index were tested via t-test for continuous variables and chi-square for categorical variables.

Ethics

The University of Puerto Rico - Medical Science Campus, Institutional Review Board (IRB) approved this study (Protocol No B0410214). Data was made available to the investigators in an anonymous format so that the identity of the beneficiaries could not be revealed.

Results

Claim level: At the claim level, a total of 5,141 hospitalization claims for CV disease with its corresponding index date were identified from January 1, 2010 to September 30, 2011. These claims were generated by 4,195 beneficiaries of the PRHIA. A total of 1,740 (33.8%) hospitalization claims had MI as the primary diagnosis, 1,860 (36.2%) HF, and 1,541 (30.0%) had stroke.

After merging the CV-related hospitalization claims data set with the NSAIDs pharmacy claims data set, it was observed that the 5,141 index dates (discharge home date) were associated with 2,091 NSAIDs claims post discharge. A total of 1,510 (72.2%) occurred more than 90 days after the index date, and 581 (29.8%) occurred within 90 days following the index date.

A total of 743 (35.6 %) NSAIDs claims occurred after an MI-related hospitalization; of which 184 (24.8%) occurred within 90 days after the index date and 59 (7.9%) within 30 days after the index date. For all HF-related hospitalizations, 565 (27.0%) NSAIDs claims were identified, 177 (31.3%) occurred within 90 days after the index date and 57 (10.1%) within 30 days after the index date. A total of 783 (37.4%) NSAIDs claims were identified after a stroke-related hospitalization; of which 220 (28.1%) occurred within 90 days after the index date and 83 (10.6%) within 30 days after the index date. Table 1 shows the distribution of NSAIDs pharmacy claims after a CV event hospitalization in the selected time period.

Table 1. Time to first NSAID claim description by CV primary diagnosis at the claim level (n=2,091).

CV-event diagnosis	Total	n (%)		
		0-30 days*	31-90 days*	>90 days*
Myocardial infarction	743 (35.6)	59 (7.9)	125 (16.8)	559 (75.2)
Heart failure	565 (27.0)	57 (10.1)	120 (21.2)	388 (68.7)
Stroke	783 (37.4)	83 (10.6)	137 (17.5)	563 (71.9)
Total	2,091	199 (9.5)	382 (18.3)	1,510 (72.2)

*Days elapsed from the CV-event index date and the first pharmacy claim for an NSAID.

Beneficiary level: A total of 774 (18.5%) beneficiaries of the PRHIA evaluated during the 2-year study period had at least one claim for an NSAID after having a CV related hospitalization. The mean age of these beneficiaries was 64.4 (SD=13.7) years old, the mean length of stay at their hospital related index date was 3.2 (SD=3.4) days, the mean time between the index date and the first NSAID prescription was 135.1 (SD=139.4) days, the mean amount of money reimbursed for the CV–event related hospitalization was $4,048 (SD=$3,820), and the majority were females (54.4%). During the study period, 654 (84.5%) had only one CV hospitalization claim, while 120 (15.5%) had two or more. The primary NSAID product associated with a post index date prescription was naproxen with 264 (34%), followed by nabumetone 239 (31%) and indomethacin 154 (20%), see table 2.

Table 2. Specific NSAIDs prescribed post index date (n=774).

NSAID	n (%)
Celecoxib	16 (2)
Ibuprofen	94 (12)
Indomethacin	154 (20)
Nabumetone	239 (31)
Naproxen	264 (34)
Salsalate	7 (1)

The primary diagnosis for the hospitalization claims of all beneficiaries who received at least one NSAID at any moment after discharge was MI for 264 subjects (34.1%), HF for 228 (29.5%) and stroke for 282 (36.4%). In total, 9.6% (401/4,195) beneficiaries with a hospitalization claim for MI, HF, or stroke, received an NSAID prescription in the immediate 90 days post-discharge. The number of beneficiaries who received at least one NSAID within the first 90 days after the index date was 127 (16.4%) for MI, 129 (16.7%) for HF and 145 (18.7%) for stroke. Table 3 shows the distribution of the first NSAID prescription according to diagnosis and the time elapsed between the index date and pharmacy claim.

Table 3. Time to first NSAID post index date stratified by CV-event diagnosis at the beneficiary level (n=774).

CV-event diagnosis	N	n (%)		
		0-30 days*	31-90 days*	>90 days*
Myocardial infarction	264 (34.1)	57 (21.6)	70 (26.5)	137 (51.9)
Heart failure	228 (29.5)	54 (23.7)	75 (32.9)	99 (43.4)
Stroke	282 (36.4)	75 (26.6)	70 (24.8)	137 (48.6)
Total	774	186 (24)	215 (27.8)	373 (48.2)

*Days elapsed from the CV-event index date and the first pharmacy claim for an NSAID.

The average time span between the index date and the first NSAID prescription was 135 (SD=139) days. For those with MI the average time span between the index date and the first NSAID prescription was 138 (SD=142) days, with HF 125 (SD=125) days, and stroke 141 (SD=148) days.

Discussion

The prevalence of NSAIDs prescribing after a CV related hospitalization in the PRHIA beneficiaries during 2010 and 2011 was assesed. A total of 774 beneficiaries with a CV-related hospitalization generated 2,091 pharmacy-claims for an NSAID post-discharge. A total of 401 beneficiaries, which represents 10% of all beneficiaries with a hospitalization claim for MI, HF, or stroke, received an NSAID prescription in the immediate 90 days post-discharge. Although the CV risks of NSAIDs are well documented in the literature, many beneficiaries are still receiving a prescription after an event.

In 2007, the American Heart Association issued guidelines discouraging the use of both, non-selective NSAIDs and COX-2 inhibitors in patients at high risk or with documented history of heart diseases (7). However, a significant amount of patients are still receiving NSAID prescriptions after a HF or MI-related hospitalization (4,15,19). In our study, 18.4% of patients received an NSAID after the CV-related hospitalization during the period of study. The lower frequency seen in this study may reflect the short duration of the study period (2 years vs. 7-10 years for other studies), and the fact that the prescription claims history was not followed beyond the 90 days after the discharge date for all the beneficiaries.

The period immediately after the occurrence of a CV event is crucial in determining outcomes. Use of appropriate medications, along with lifestyle modifications is necessary to decrease morbidity and mortality associated with these diseases. Medications claimed during the immediate 90 days after the discharge, and especially within the first 30 days, represent the first prescriptions that the patient picks up at the pharmacy after the event, which should include evidence-based therapies indicated to decrease morbidity and mortality (e.g. beta-blockers, angiotensin converting enzyme inhibitors or angiotensin receptor blockers, diuretics, aspirin, etc.). NSAIDs can counteract the efficacy of these antihypertensive medications, inducing an increase in blood pressure by inhibiting prostaglandin-mediated vasodilation, which may in turn cause an increase in cardiac afterload and a reduction in cardiac contractility and cardiac output. NSAIDs can also promote sodium and fluid retention (11,25). These deleterious effects may result in HF exacerbation (26). In addition, the well-described thrombotic effects of NSAIDs can increase the risk of MI and stroke. Concomitant use of nonselective NSAIDs may also interfere with the cardioprotective effects of aspirin, commonly prescribed as secondary prevention (11).

In our study naproxen, which is the NSAID with the safest CV profile, was the NSAID with the most pharmacy claims generated after the index date, (34.11%). Diclofenac, which has been associated with a higher CV risk, is not included in the insurer's drug formulary.

Traditionally, CV risks of NSAIDs have been associated with higher doses and duration of therapy. Current recommendations for the use of NSAIDs in patients with established CV disease are to be cautious and use the lowest dose for the shortest amount of time possible. Recent studies have challenged this recommendation, as an increased risk of CV-related death and decompensation has been proved even after short-term use of NSAIDs (less than 7 days)(18). In this study we did not measure the amount of time beneficiaries used the NSAIDs, as current clinical evidence suggests that any use is associated with an increased risk.

In 2012, the Centers for Medicare and Medicaid Services (CMS) implemented a Readmissions Reduction Program to reduce payments to hospitals with excess readmissions from specific conditions such as MI and HF (27). Since then, great effort has been made to determine strategies to decrease readmission rates. Effective strategies that have been documented in the literature include identification and avoidance of factors that may increase the risk of readmission, as well as the development and proper communication of evidence-based medication plans (28). The fact that in our study approximately 10% of all patients with a CV-related hospitalization had a pharmacy claim for an NSAID within 90 days post-discharge highlights the need for a better medication plan and reconciliation to decrease hospital readmissions. One limitation of this study is the fact that the pharmacy claims do not necessarily reflect new prescriptions and may include refills the pharmacy processed during the study period. Until it is further clarified, the problem of NSAIDs prescription after a CV event should be considered a multifactorial problem, as physicians, nurses, pharmacists, and medical insurance companies play an equally important role. Better communication strategies between healthcare professionals and patients are needed. Community pharmacists should get involved in performing medication reconciliation after a hospitalization to prevent filling or refilling medications that could have been important factors of CV disease in the first place. The medication plan should be clearly communicated to the patients and their families. Lastly, medical insurance companies should implement strategies for safer use of potentially harmful medications by their beneficiaries.

Conclusion

Ten percent (10%) of all beneficiaries who were hospitalized for a CV event received an NSAID in the immediate 90 days after the discharge date. It represents a major challenge to the healthcare system, as it may reflect unawareness on the impact of proved evidence in making clinical decisions. Many studies have been published establishing the relationship between NSAIDs and cardiovascular events and clinical guidelines have incorporated this information in their recommendations (1,3-5,7-9,11,14-19,24). The FDA has included specific statements in the package inserts and drug facts labels of NSAIDs warning healthcare professionals and patients about the potential risks of such medications in patients with established cardiovascular disease.6 Still, many patients receive a prescription for NSAIDs

after a CV event. The high prevalence of NSAID prescription after a CV related hospitalization demonstrates that initiatives to promote the discontinuation of this practice are needed. The results of this study provide a foundation for the development of evidence-based guidelines for the safe management of pain in patients with established CV diseases. Availability and ease of access of NSAIDs should be considered when creating awareness of prescribing patterns and CV outcomes.

Further research may be conducted to determine if beneficiaries who received an NSAID after a CV hospitalization were subsequently readmitted.

Limitations of the project

One limitation of this study is that we could not identify prescribed NSAIDs that were not included in the drug-formulary of the health insurance company or that were denied because of prior-authorization criteria. Beneficiaries who acquired a non-formulary NSAID or an OTC formulation couldn't be included. The results of this study represent the reality of the clinical practice where drug selection and utilization is determined by a closed limited drug formulary. Additionally, this study does not account for beneficiaries who died after the event during the study period, which may result in an underestimate rate of patients who received an NSAID after the event during the study period.

Resumen

Objetivo: Los antiinflamatorios no-esteroidales (NSAIDs, por sus siglas en inglés) se utilizan para manejar dolor e inflamación. Estos asocian a riesgo cardiovascular que incluye infarto, apoplejía y fallo cardiaco. En el periodo de tiempo inmediato luego de un evento cardiovascular es necesario modificar la terapia farmacológica para disminuir morbilidad y mortalidad. El objetivo de este estudio es medir prevalencia de prescripción de NSAIDs en los 90 días inmediatos a una hospitalización por eventos cardiovasculares en beneficiarios de Medicaid en Puerto Rico. Metodología: Se identificaron beneficiarios con alguna reclamación para hospitalización con un diagnóstico primario de evento cardiovascular (fallo cardiaco, apoplejía, infarto) durante el periodo de estudio. Se utilizó el historial de reclamaciones de farmacia para evaluar ocurrencia de prescripción de NSAIDs luego del alta. Resultados: Un total de 4,195 beneficiarios tenían al menos una reclamación de hospitalización por evento cardiovascular. De estos, 774 (18.5%) tenían al menos una reclamación para un NSAID luego del alta durante el periodo de estudio, y 401 (9.6%) en los 90 días luego del alta. El tiempo promedio entre la fecha del alta y la primera reclamación por un NSAID fue 135 días. Conclusión: Cerca de 20% de todos los beneficiarios que fueron hospitalizados por un evento cardiovascular recibieron receta para un NSAID durante el periodo de estudio. Aproximadamente 10% de los beneficiarios recibieron la receta durante los 90 días inmediatos al alta. Esto representa un reto mayor al sistema de salud ya que puede reflejar desconocimiento del impacto de estos medicamentos en los resultados de salud.

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Appendix A. List of ICD-9s codes used to identify CV-events related hospitalizations and their corresponding description.

ICD-9s number	ICD-9s description
Myocardial infarction	
410.01	AMI of Anterolateral Wall Initial Episode of Care
410.11	AMI of Other Anterior Wall Initial Episode of Care
410.2	AMI of Inferolateral Wall Episode of Care Unspecified
410.21	AMI of Inferolateral Wall Initial Episode of Care
410.41	AMI of Other Inferior Initial Episode of Care
410.51	AMI of Other Lateral Wall Initial Episode of Care
410.61	True Posterior Wall Infarction Initial Episode of Care
410.7	Subendocardial Infarction Episode of Care Unspecified
410.71	Subendocardial Infarction Initial Episode of Care
410.72	Subendocardial Infarction Subsequent Episode of Care
410.81	AMI of Other Specified Sites Initial Episode of Care
410.9	AMI of Unspecified Site Episode of Care Unspecified
410.91	AMI of Unspecified Site Initial Episode of Care
Heart failure	
428	Congestive HF Unspecified
428.1	Left HF
428.2	Unspecified Systolic HF
428.21	Acute Systolic HF
428.23	Acute on Chronic Systolic HF
428.3	Unspecified Diastolic HF
428.31	Acute Diastolic HF
428.33	Acute on Chronic Diastolic HF
428.4	Unspecified Combined Systolic and Diastolic HF
428.41	Acute Combined Systolic and Diastolic HF
Stroke	
430	Subarachnoid Hemorrhage
431	Intracerebral Hemorrhage
432.1	Subdural Hemorrhage
433.1	Occlusion and Stenosis of Carotid Artery without Cerebral Infarction
433.11	Occlusion and Stenosis of Carotid Artery with Cerebral Infarction
434.91	Cerebral Artery Occlusion Unspecified with Cerebral Infarction