# Post Marketing Safety Data Analysis Reveals Increased Propensity for Severe Cardiovascular and Cerebrovascular Side Effects in Patients Taking Celecoxib Compared to Other NSAIDs

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## ABSTRACT

Non-steroidal anti-inflammatory medications, NSAIDS, are commonly used worldwide for their analgesic and anti-inflammatory properties, and are deemed safe for over the counter access. NSAIDS as a class have been associated with cardiovascular, CV, cerebrovascular, CVA, and hypertension, side effects, with rofecoxib being removed from the market due to these toxicities. However, the risks of heart attack and stroke were deemed similar in all currently marketed NSAIDs. The growing concern over the potentially fatal CV and CVA warranted further studies to quantify the associations these side effects. Here, we analyzed over twelve million reports in the FDA Adverse Event Reporting System, FAERS, to evaluate the reporting odds ratios of hypertension, myocardial infarction, and stroke in patients taking individual NSAIDs and acetaminophen as monotherapy. We found that the risk of CV and CVA ADRs was 10-200 fold higher for celecoxib, when compared to ibuprofen, naproxen, meloxicam, ketoprofen, diclofenac and acetaminophen. Additionally, male patients taking celecoxib were at a nearly two-fold higher risk of myocardial infarction.

## BACKGROUND AND PURPOSE

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed drugs worldwide. They are used by over thirty million people daily seeking their anti-inflammatory and pain relieving properties[1]. They work by selectively inhibiting the cyclooxygenase (COX) enzymes, of which there are two isoforms. COX-1 plays a protective role and is present in many tissues, maintaining platelet activity, kidney functions, and protection of stomach mucosa[3]. On the other hand, COX-2 is present at sites of inflammation. In recent years, NSAIDs have come into the light due to their serious, life-threatening adverse effects, particularly the negative cardiovascular effects. Randomized clinical trials were performed and found an increased risk of stroke, MI, and HTN associated with particularly celecoxib use. This promoted the FDA to include a black box warning in 2007. To date, the relationship between NSAID and non-NSAID use and its effects on heart attack, stroke, and hypertension remains largely unclear and warrants further research. The previous studies showed conflicting evidence, which warrants further studies of post marketing ADR reports. It was necessary to expand on the evidence and introduce clarity on potentially fatal ADRs of these commonly used medications. In this study, we analyzed 120,707 FAERS database reports to analyze the relationship between NSAID use and cardiovascular adverse effects, namely hypertension (HTN), cerebrovascular accident (CVA), and myocardial infarction (MI).

## METHODS

In this study, 102,702 reports were selected. Patients 18 years of age and older taking the following NSAIDs, ibuprofen, meloxicam, celecoxib, diclofenac, ketorolac, and non-NSAID medication, acetaminophen, as monotherapy were selected into cohorts. Patients with heart conditions such as coronary artery disease were excluded. The NSAID group contained 100,202 reports and the non-NSAID group contained 20,700 reports. CV and CVA adverse drug events frequencies were calculated: celecoxib n=20,614, meloxicam n=1753, ibuprofen n=27,037, naproxen n=34,644, diclofenac n=14,866, ketorolac n=1288, and acetaminophen n=20,700. Frequencies of MI, HTN, and CVA were reported for NSAIDs and compared to non-NSAID pain medications (Fig. 1). We also analyzed male and female reports of CV adverse events among Celecoxib users (Fig. 3).

## RESULTS

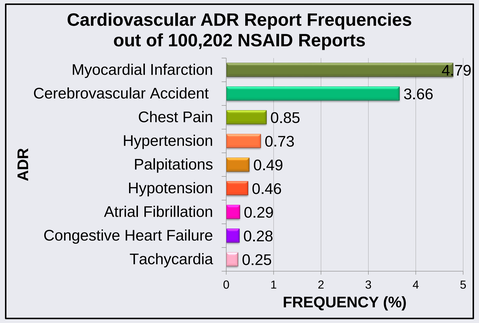
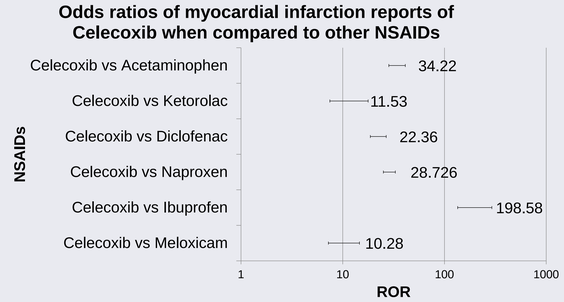
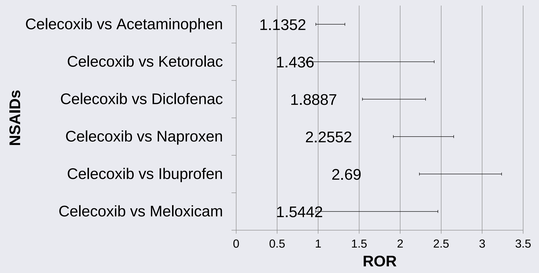



**Fig. 1. Top Cardiovascular ADRs in patients taking NSAIDs for pain**



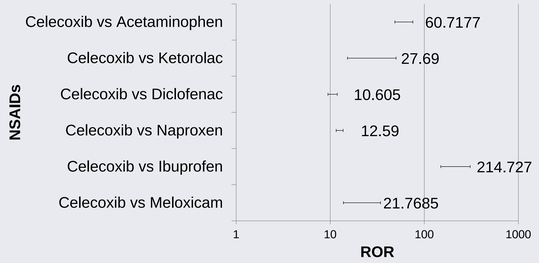




**Fig. 2. Odds ratios of cardiovascular ADRs.** Odds ratios were calculated by comparing MI, HTN, and stroke ADRs of Celecoxib to other NSAID pain medications.

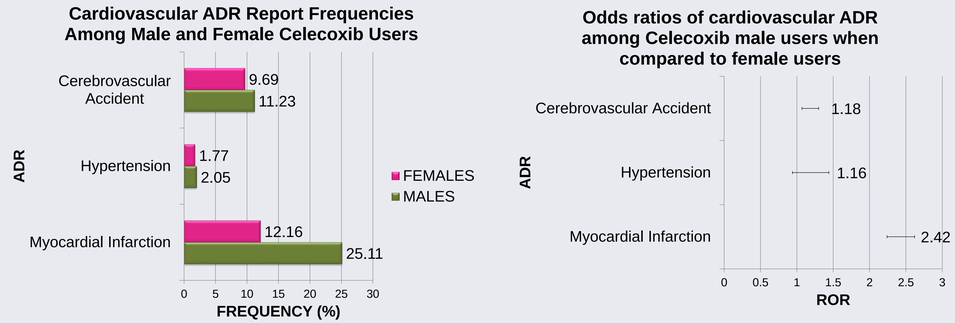



**Fig. 3. Celecoxib ADRs among male and female users**. a) Frequencies of CVA, HTN, and MI were calculated between male and female Celecoxib users. b) Odds ratios were performed among male users when compared to females for the three ADRs.

## CONCLUSIONS

Overall, our results revealed that NSAIDs had a significantly higher risk of cardiovascular adverse effects when compared to non-NSAID pain medications. Out of these NSAID medications, Celecoxib exhibited the highest rates of MI, HTN, and CVA adverse effects. In addition, male Celecoxib users had a higher risk of all three of these adverse effects when compared to female users, the highest being myocardial infarction. The FDA has released and changed the Celecoxib label slightly over the past few years after adding a BBW 2007, a black box warning was added to the label to warn consumers about the potential cardiovascular risks associated with Celecoxib use while stating that “all NSAIDs may have a similar risk.” However, in 2016, the black box warning was slightly altered, reporting that “based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. Our study has demonstrated that the CV risk for all NSAID pain medications is not similar and that Celecoxib has a significantly higher risk when compared to the other more commonly prescribed NSAIDs. Finally, this study aimed to provide more clarity to the FDA drug label put forth on Celecoxib and its potentially life-threatening adverse effects. It highlights the necessity of exercising caution while prescribing this medication and also urges consumers to use Celecoxib for the shortest duration possible, or perhaps even use other NSAIDs which have been well studied and have fewer known adverse effects.

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## ACKNOWLEDGEMENTS

This work was supported by a Skaggs Scholarship from the UC San Diego Skaggs School of Pharmacy and Pharmaceutical Sciences