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Investigating The Cardiovascular Effects Of Celecoxib In The Presence Of Heart Failure

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Abstract

Cardiovascular risk seems to be elevated with using cyclooxygenase-2 inhibitors, according to both observational studies and randomized trials. Neither the dosage of celecoxib nor the patient's cardiovascular health before to therapy could be adequately evaluated in previous placebo-controlled randomized trials. Our objective was to evaluate the risk of cardiovascular events associated with three different doses of celecoxib and to determine whether or not there was a correlation between preexisting cardiovascular risk and the drug's influence on cardiovascular events. Primary end goal was a composite of cardiovascular-related deaths, MIs, strokes, heart failure, and thromboembolic complications. The hazard ratio for the combined dosages studied was 1.6 (95% CI, 1.1 to 2.3) after 16 070 patient-years of follow-up. We found indications of dose- and risk-based cardiovascular differences in response to celecoxib.

Keywords: drugs; cardiovascular diseases; cyclooxygenase 2 inhibitors

INTRODUCTION

Celecoxib is a nonsteroidal anti-inflammatory medication (NSAID) selective for cyclo-oxygenase-2 (COX-2), and Inflammatory disorders such arthritis, rheumatoid arthritis, ankylosing spondylitis, adult acute pain, and familial adenomatous polyposis are all treated with this drug. 1 By binding to the membrane protein COX-2, celecoxib blocks the generation of prostaglandins, which is its primary mode of action. Because of its specificity for COX-2, celecoxib prevents the gastrointestinal injuries common to those taking nonselective NSAIDs. A decreased risk of severe gastrointestinal damage has been linked to the use of coxibs, according to controlled research. 2 While this is a significant improvement over nonselective NSAIDs, it has been reported that coxibs can cause gastrointestinal (GI) side effects, especially with long-term use, and that their use in addiction is linked to a higher risk of cardiovascular side effects like heart attack, stroke, and even heart failure. In reality, celecoxib's mechanism of action is reliant on the drug's interaction with the constituents of biological membranes.

To what degree celecoxib shares rofecoxib's elevated risk of cardiovascular events, the COX-2 selective inhibitor, is a source of heated discussion. The clinical studies that have been conducted on celecoxib have not been adequately powered, and their primary purpose has not been to establish the danger to the cardiovascular system. In addition, the results of the studies that have provided data on cardiovascular events seem to be inconsistent with one another. Both observational and randomized trial data point to the possibility of a dose-related5 relationship between coxib-associated cardiovascular risk and the dosage interval. 10 To yet, there haven't been enough cardiovascular events in clinical studies including celecoxib to determine whether or not the risk of cardiovascular complications increases or decreases depending on a patient's preexisting cardiovascular condition.

LITERATURE REVIEW

Cheng B-R, et al. (2019), Celecoxib was compared to other non-selective NSAIDs and a placebo for its effect on the cardiovascular system. In individuals with rheumatoid arthritis and osteoarthritis, Studies comparing oral celecoxib to a nonselective NSAID or a placebo were considered. We looked through databases in the East and West, in China, and in the People's Republic of China. Both study selection and data extraction were done independently by two authors. In order to assess the likelihood of bias, we employed the Cochrane risk-of-bias Tool for Randomized Trials. The risk ratio and 95% confidence interval for the impact size were presented. Celecoxib's safety in individuals with rheumatoid arthritis and osteoarthritis does not seem to be dose- or time-dependent. Nevertheless, whether this holds true for aspirin-treated individuals and those with preexisting cardiovascular disease is still up for debate.

F. Al-Rashed; D. Calay; M. Lang; etc (2018), Recent research implicates rofecoxib, and celecoxib looks equal to NSAIDs naproxen and ibuprofen, although there is still worry about the athero-thrombotic risk presented by cyclo-oxygenase (COX)-2-selective inhibitors. Celecoxib has been hypothesized to improve vascular endothelial protection via activating AMP kinase (AMPK) signaling, and this is what we set out to test. Celecoxib induced CREB and Nrf2 activation, while ibuprofen and naproxen did not elicit similar responses, and knocking down AMPK prevented this. Celecoxib activated AMPK, which in turn suppressed TNF—induced NF-B p65(Ser536) phosphorylation. DMC replicated this reaction, although ibuprofen and naproxen did not. This action inhibited VCAM-1 expression through inducing HO-1. In a similar vein, celecoxib inhibited IL-6 induction through IL-1. Patients taking celecoxib may be at reduced risk for cardiovascular disease due to the drug's ability to increase vascular protection through AMPK-CREB-Nrf2 signaling. The development of safer anti-inflammatory medicines requires an understanding of NSAID heterogeneity and COX-2-independent signalling.

Almoallim, H., Ali, R.A., and Halabi, H. (2019), It's crucial to talk about how common cardiovascular diseases (CVD) are among people with rheumatologic conditions. While there is overlap amongst diseases owing to shared common risk factors, which may be associated to increased longevity as a result of recent treatment developments, each illness has its own own set of symptoms. By practice like this, the distinctive cardiac presentation of each rheumatologic disease may be identified. Due to low life expectancy, few treatment approaches, a lack of clarity about the pathogenic processes at play in each illness, and an absence of reliable diagnostic tools, this was formerly impossible.

Rajeshwary Ghosh, (2015), The most often prescribed medications in the world are nonsteroidal anti-inflammatory drugs (NSAIDs). Pain, rheumatoid arthritis, and musculoskeletal diseases are only some of the many ailments treated with NSAIDs. It is generally accepted that NSAIDs have positive effects, including pain reduction or relief, inflammatory reduction, and anticancer properties. Some of the negative consequences of NSAIDs include ulcers, internal bleeding, renal failure, and an increased risk of heart attack and stroke. Several cell types, including those involved in the heart and blood vessels, have demonstrated evidence of NSAID-induced reactive oxygen species (ROS). Apoptosis is one of these crucial mechanisms that, when highly active, results in cell death. The significance of NSAID-induced reactive oxygen species (ROS) in CVD and the association between NSAIDs and CVD are discussed in this study.

Shanzana Khan, (2019). In the West, cyclo-oxygenase (COX) inhibitors are often used as pain relievers and anti-inflammatory medications. Yet, it is also well-known that they raise the danger of heart attacks and strokes. Newly worrying information suggests that this impact may occur even with acute consumption, giving this field additional relevance. Yet, Vasodilation and improved vascular function are two of the many benefits associated with inhibiting cyclooxygenase (COX), and aspirin has been used for decades as a standard in cardiovascular preventative medicine. Here, we provide a comprehensive summary of the most recent findings in the preclinical and clinical literature on COX inhibitor cardiotoxicity.

METHODS

We predetermined the following characteristics of the trials that would be included in the study before beginning data collection: The studies would be placebo-controlled, randomized, and would follow participants for at least three years. We contacted the National Institutes of Health and Pfizer whether they knew of any unpublished studies that fit the description and examined the public literature. The search turned up four other studies, in addition to APC and PreSAP. Celecoxib's therapeutic potential was investigated in all studies meeting these two criteria, but not for arthritis.

Procedures

Patient-level data including randomization code, baseline clinical characteristics, period of follow-up, and data on events to be categorized were supplied to Statistics Collaboration by each participating study after the statistical analysis technique was authorized. We reclassified certain baseline variables in accordance with the planned patient-level meta-analysis, even though each trial gathered various forms of such data.

Two cardiovascular experts with prior expertise adjudicating cardiovascular end points made up the adjudication committee. Each study's research team compiled a summary of potential CV or CVA events and provided it to the reviewers. For the purpose of adjudication, we standardized our endpoint definitions. 15 Reviewers were blinded to treatment assignment and assigned probabilities and certainty ratings to each occurrence based on the quality and quantity of supporting evidence.

Statistical Analysis

As was previously explained, the main analysis of each trial was a hierarchical classification of composite outcomes, with events added to the hierarchy as the subjectivity of diagnosis increased. Predetermined cardiovascular mortality, myocardial infarction, stroke, heart failure, or thromboembolic event composite was to be reported as the main outcome of this research.

To conduct our predetermined analysis, we separated the 6 trials into their respective treatment groups and counted the number of occurrences of each outcome and the rate per 1000 patient-years for each. To calculate the hazard ratio and 95% confidence intervals for each dose group of celecoxib vs the placebo group in the same trial, we used Cox models stratified by the study-specific strata. Celecoxib's overall safety and dose-dependent safety were both assessed in meta-analyses. Antilog of the pooled log hazard ratio was used to estimate the hazard ratio for celecoxib's systemic effect; this was obtained by averaging the log hazard ratios from each trial and weighting the results by the inverse of their variance. This estimate was double-checked by comparing the outcomes of a Cox model stratified by trial and baseline aspirin usage to those of a typical Mantel-Haenszel pooling odds ratio; if either of these analyses yielded significantly different results from the primary method, we intended to investigate potential causes of discrepancy.

We organized research into the following categories based on dosing regimen in order to evaluate its impact: The Celecoxib/Selenium experiment and the PreSAP study used a 400 mg once-daily dosage; the ADAPT, APC (low dose), and CDME studies used 200 mg twice-daily; the MA27 study used 400 mg once-daily. To further understand the effects of celecoxib and placebo, we primarily used an intention-to-treat analysis, which included monitoring participants for cardiovascular events for as long as they stayed in the research.

By adapting the components in the Framingham Heart Study risk model to the availability of data from these studies, we were able to develop a "3-category" risk score: Low risk is defined as the absence of risk factors, moderate risk as the presence of one or more of the following, and high risk as the presence of diabetes. Since

relatively few study participants were in the lowest-risk group, we reclassified the risk score from its original 4 categories to 3 categories in our analysis. As current smoking status was not a data collection priority for the MA27 trial, we made the assumption that no participants were smokers. In the Celecoxib/Selenium Study, we were unable to determine whether or not participants used medication to decrease their cholesterol levels; in that trial, With total cholesterol >240 mg/dL, low-density lipoprotein cholesterol >160 mg/dL, or a total/HDL cholesterol ratio >5, hyperlipidemia was diagnosed. We planned to employ the risk score in two separate ways in our analysis. We also analyzed how preexisting aspirin consumption influenced celecoxib danger.

Results

There were noteworthy variances in the baseline characteristics of the 6 trials (Table 1). Patients in the ADAPT study were older than those in the other trials (mean age of 75 vs. 61) while patients in the CDME study were more culturally diverse (67 percent white vs. almost 95 percent white). Patients in the CDME study were all diagnosed with diabetes, while the other studies had a prevalence of diabetes about 10%. The studies had varying baseline cardiovascular risk. All participants in the CDME study had diabetes, which put them all at a high risk for cardiovascular problems. Patients in the ADAPT study had the greatest cardiovascular risk, followed by the Celecoxib/Selenium Trial, in part because they were all at least 70 years old. The high rates of low-dose aspirin usage in CDME and ADAPT likely reflect the higher cardiovascular risk in these patient populations.

Table 1: Common Baseline Characteristics Across Trials

Baseline Characteristic	ADAPT (n=1809; 3530 patient-years)	APC (n=2035; 6234 patient-years)	CDME (n=86; 101 patient-years)	MA27 (n=1635;* 695 patient-years)	PreSAP (n=1561; 4141 patient-years)	Celecoxib/Selenium (n=824;† 1369 patient-years)	Total (n=7950; 16 070 patient-years)
Age, mean (SD), y	75 (4)	59 (10)	59 (9)	64 (9)	60 (10)	63 (9)	64 (10)
Male, n (%)	979 (54)	1387 (68)	53 (62)	0	1035 (66)	559 (68)	4013 (50)
Race, n (%)							
White	1753 (97)	1863 (92)	58 (67)	1503 (94)	1392 (89)	778 (96)	7347 (93)
Black	24 (1.3)	112 (5.5)	19 (22)	54 (3.4)	34 (2.2)	16 (2.0)	259 (3.3)
Asian	8 (0.4)	15 (0.7)	3 (3.5)	26 (1.6)	96 (6.1)	12 (1.5)	160 (2.0)
Other	22 (1.2)	45 (2.2)	6 (7.0)	8 (0.5)	39 (2.5)	4 (0.5)	124 (1.6)
Diabetes, n (%)	133 (7.4)	194 (9.5)	86 (100)	100 (6.1)	159 (10)	62 (7.5)	734 (9.2)
HTN or on anti-HTN	725 (40)	834 (41)	53 (62)	561 (34)	582 (37)	297 (36)	3052 (38)
medication, n (%)							
Hyperlipidemia† or on	589 (33)	769 (38)	47 (55)	280 (17)	269 (17)	270 (33)‡	2224 (28)
lipid-lowering medication, n (%)							
Current smoker, n (%)	55 (3.0)	337 (17)	Not collected	Not collected	368 (24)	79 (16)	839 (14)
Low-dose aspirin use, n (%)	907 (50)	637 (31)	53 (62)	226 (14)	268 (17)	370 (45)	2461 (31)
Prior CV event,§ n (%)	232 (13)	292 (14)	1 (1.2)	113 (6.9)	198 (13)	116 (14)	952 (12)
Low CV risk, n (%)	261 (14)	491 (24)	0	820 (50)	506 (32)	154 (19)	2232 (28)
Moderate CV risk, n (%)	477 (26)	582 (29)	0	372 (23)	480 (31)	252 (31)	2163 (27)
High CV risk, n (%)	1071 (59)	962 (47)	86 (100)	443 (27)	575 (37)	418 (51)	3555 (45)

The combined follow-up time for all trials was 16 070 patient-years. Depending on the experiment, this ranged from 101 (CDME) to 6234 (APC) patients-years. (Table 2). The length of time between trials was a significant variable. Three-year follow-up rates were 90% in APC and 43% in PreSAP. In contrast, ADAPT, the Celecoxib/Selenium Study, CDME, and MA27 all had shorter median follow-up periods of 24, 21, 15, and 5 months, respectively.

Table 2 displays the incidence of adverse events and the corresponding hazard ratios for the primary composite end point across all trials. With 86 individuals and a placebo group that had 3 major composite end points and a celecoxib group that experienced none, the CDME trial had the lowest rate of events.

Table 2. Event Rates per 1000 Patient-Years and Pooled Hazard Ratios

Study	Median Follow-Up Time, mo	Events/Participants		Event Rate/1000 patient-y		Hazard Ratio	95% CI	Relative Weight*
		Placebo	Celecoxib	Placebo	Celecoxib			
400 mg QD								
PreSAP	36	12/628	23/933	7.2	9.4	1.3	0.6–2.5	7.9
Selenium/Celecoxib	21	8/410	7/414	11.8	10.3	0.9	0.3–2.4	3.7
Pooled	35	20/1038	30/1347	8.6	9.6	1.1	0.6–2.0	
200 mg BID								
ADAPT	24	18/1083	18/726	8.6	12.8	1.5	0.8–2.9	9.0
APC	37	8/679	20/685	3.9	9.7	2.5	1.1–5.7	5.7
CDME	15	3/47	0/39	54.3	0.0	0.0	· · ·	0.0
Pooled	36	29/1809	38/1450	6.9	10.8	1.8†	1.1–3.1†	
400 mg BID								
APC	37	8/679	27/671	3.9	13.4	3.6	1.6–8.0	6.2
MA27	5	3/817	6/818	8.7	17.2	1.8	0.4–7.3	2.0
Pooled	11	11/1496	33/1489	4.6	13.9	3.1	1.5–6.1	
Pooled all doses	31	52/3664§	101/4286	7.5	11.2	1.6‡	1.1–2.3‡	

When all dosing regimens were included, including the CDME trial, cardiovascular mortality, myocardial infarction, stroke, heart failure, or thromboembolic events had a pooled hazard ratio of 1.6. Estimates of the pooled hazard ratio were quite similar whether we employed Cox regression, the inverse variance approach, or the Mantel-Haenszel estimate.

Effect of Dose

After accounting for confounding factors such age, gender, and baseline cardiovascular health, the hazard ratios for each dose group were calculated. Doses administered twice daily were more dangerous than once daily ones. Due to the small number of events in the CDME trial, we repeated the analysis with and without those data and found strikingly comparable findings for both the overall hazard ratio and the specific hazard ratios based on dosage.

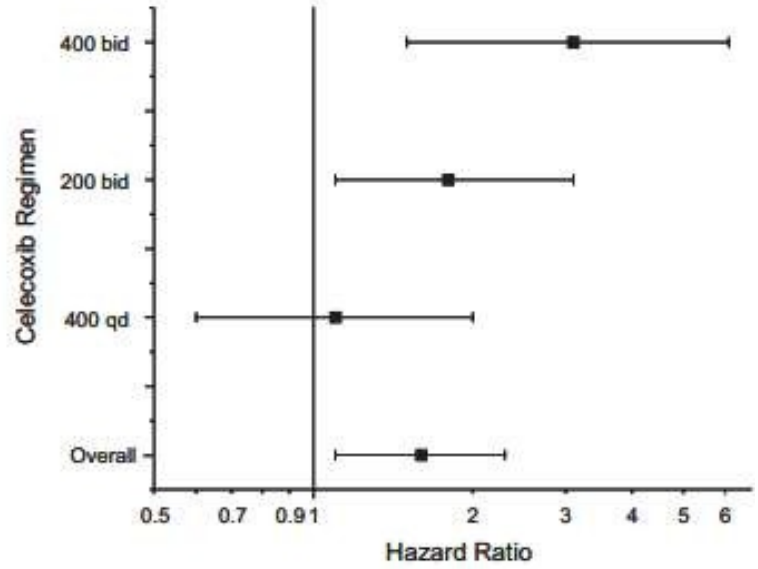

Figure 1. Hazard ratios for each dose regimen and the combined

Effect of Baseline Cardiovascular Risk

Overall, the incidence of adverse events increased across all three categories of preexisting risk with celecoxib usage (Figure 2). Celecoxib's hazard ratio over placebo was 1.7 after controlling for baseline risk, which is very close to the pooled estimate that did not account for baseline risk. When all dosages of celecoxib were considered together, there was some evidence for an interaction between usage and baseline risk for outcomes; there was more evidence for such an interaction when the 3 dose regimens were ordered into a model, with the highest-risk individuals showing the most danger from using celecoxib (Figure 2). Whether or whether the patient took aspirin before taking celecoxib, the risk rose.

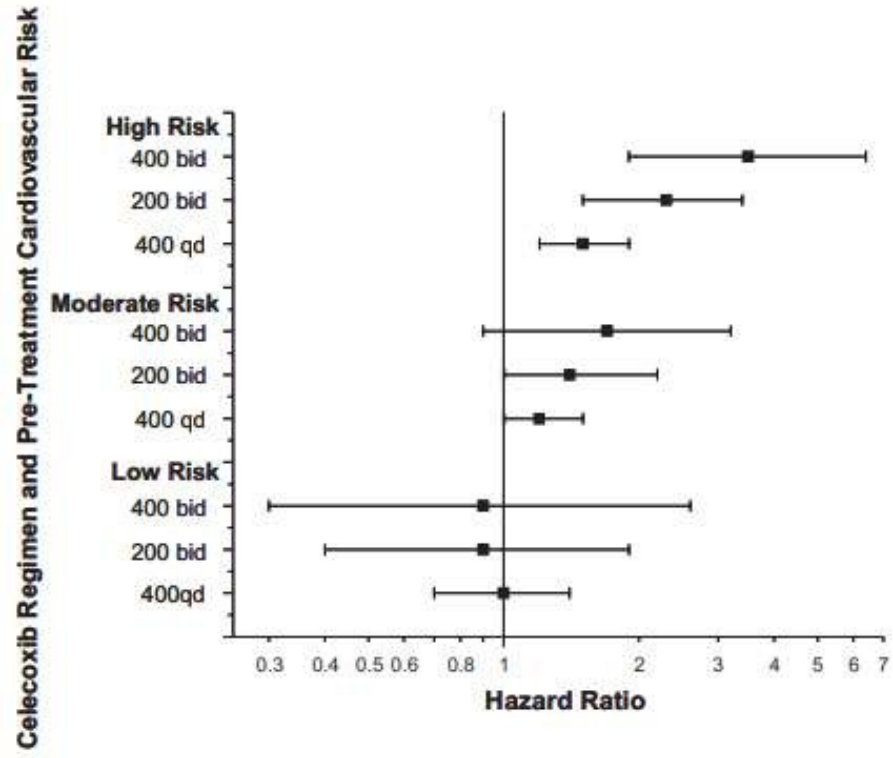

Figure 2. Relationship between celecoxib dose.

Discussion

The findings reveal that the detrimental impact of dosage is more prominent in higher-risk individuals, and that there is evidence of an interaction between baseline cardiovascular risk and the dosage of celecoxib, and that there are dose and regimen changes in risk. The larger sample size in this investigation improves our understanding of the importance of both dosage and baseline cardiovascular risk in the development of celecoxib-related adverse events. Since celecoxib is the sole FDA-approved coxib and the most widely used COX-2 inhibitor internationally, it is the only option for patients in the United States, which carries a black-box warning from the Food and Drug Administration, these results have substantial bearing on how coxib-beneficial patients should be treated.

Because coxibs inhibit COX-2-generated prostacyclin without also inhibiting thromboxane synthesis, there is an imbalance between these two cytokines, is one of the most hotly contested strategies of promoting cardiovascular risk. There are many methods through which NSAIDs, such as coxibs and other nonsteroidal anti-inflammatory drugs, might raise blood pressure (20,21). More trials and events are included in this study than in placebo-controlled studies, which helps quantify the effect of dosage and regimen on celecoxib risk. The 400 mg once day dosage was associated with a lower risk in previous research (PreSAP), and the Celecoxib/Selenium Study, which examined the same dosage schedule, confirmed this conclusion with an even lower point estimate. The wide confidence intervals (CIs) around the overall point estimate for the 400-mg-QD dosage suggest that the absence of danger at this dose cannot be ruled out. Our findings are consistent with the latest scientific position statement from the American Heart Association, which recommends the lowest effective dosage of celecoxib for all patients, but particularly those at greater risk. In fact, even in the lowest-risk categories, we cannot rule out a risk increase of up to 50% in the 400-mg-QD dosage group and a risk increase of roughly 3-fold in the 400-mg-BID dose group. We also owe a great deal to the long-term data collected by ADAPT, APC, and PreSAP.

CONCLUSION

A pooled study of 16,000 patient-years of data from six randomized studies of celecoxib vs placebo, suggests that the dosage schedule for celecoxib affects the risk. The results demonstrated an interaction between preexisting cardiovascular risk and the effects of celecoxib, with patients at increased risk of adverse cardiovascular events after starting treatment with the drug. These results can assist guide reasonable clinical judgments about celecoxib usage, even if the dosages studied were greater than those used for the most prevalent diseases for which celecoxib is given in the United States.

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