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ORIGINAL ARTICLE

Cardiovascular Safety of Celecoxib after Cardiac Surgery with Cardiopulmonary Bypass: A Retrospective Cohort Study

Isao Nahara[1], Masato Takeuchi[1], Shiro Tanaka[2], Hiroshi Yonekura[1,3], Chikashi Takeda[1,4], Koji Kawakami[1]

ABSTRACT

BACKGROUND

Cardiac surgery is a highly invasive procedure resulting in hypercoagulability due to thoracotomy and cardiopulmonary bypass (CPB). The long-term use of selective cyclooxygenase-2 inhibitors has been shown to increase the risk of adverse cardiovascular (CV) events such as myocardial infarction. This study aimed to determine whether short-term prescription of celecoxib increases CV events in patients who have undergone cardiac surgery with CPB.

METHODS

This retrospective observational study included 16,141 patients (≥20 years) who had undergone cardiac surgery with CPB between April 1, 2008 and March 31, 2016. Patients who underwent coronary artery bypass grafting were excluded. Patients who received celecoxib (n = 904) and acetaminophen (n = 5,002) from postoperative day 0 to 30 were extracted and matched by propensity score (PS). The primary outcomes were all-cause death and CV events, defined as coronary artery disease, ischemic stroke, pulmonary embolism, and venous thrombosis, coded using International Classification of Diseases-10 within 30 days after the first postoperative prescription of either medication. Results were assessed using Kaplan-Meier survival analysis and multivariate Cox regression analysis.

RESULTS

PS matching created 885 pairs. Multivariate Cox regression analysis showed that prescription of celecoxib after cardiac surgery was not associated with an increase in the primary outcomes when compared with prescription of acetaminophen (hazard ratio, 0.76; 95% confidence interval, 0.35–1.65).

CONCLUSIONS

The prescription of celecoxib in patients who had undergone cardiac surgery with cardiopulmonary bypass was not statistically different from the prescription of acetaminophen in the incidence of CV events and death.

KEY WORDS

Celecoxib, Cardiac surgery, Cardiopulmonary bypass, Acetaminophen, Cyclooxygenase-2 inhibitors

[1] Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University
[2] Department of Clinical Biostatistics, Graduate School of Medicine, Kyoto University
[3] Department of Clinical Anesthesiology, Graduate School of Medicine Faculty of Medicine, Mie University
[4] Department of Anesthesia, Kyoto University Hospital

Corresponding author: Koji Kawakami
Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, YoshidaKonoecho, Sakyoku, Kyoto 6068501, Japan
E-mail: kawakami.koji4@kyoto-u.ac.jp

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BACKGROUND

Pain management after cardiac surgery is fundamental to patient care. Multimodal analgesia, which is the use of a combination of drugs that exhibit different analgesic mechanisms of action, is the optimal strategy for perioperative analgesia. Nonsteroidal anti-inflammatory drugs and acetaminophen are commonly included in multimodal analgesic protocols; the benefits of these medications in pain management have been well described [1, 2].

Celecoxib is a selective cyclooxygenase-2 (COX-2) inhibitor that is superior to acetaminophen in pain relief and has a comparable analgesic effect to traditional nonsteroidal anti-inflammatory drugs [3]. A previous study reported that celecoxib is an effective postoperative analgesic in thoracic surgery [4]. Celecoxib has the advantage of inducing less gastrointestinal dysfunction compared with classical nonsteroidal anti-inflammatory drugs [5]. However, inhibiting prostacyclin and prostaglandin E2 in blood-vessel walls with selective COX-2 inhibitors, without concomitant thromboxane A2 inhibition, could promote hypertension and thrombosis and increase cardiovascular (CV) risk [6]. Indeed, long-term use of selective COX-2 inhibitors has been shown to increase the risk of adverse CV events, such as myocardial infarction [7–10]. Furthermore, short-term use of the COX-2 inhibitor valdecoxib and its intravenous prodrug parecoxib after a coronary artery bypass graft (CABG) are associated with an increased incidence of CV events [11]. Consequently, celecoxib use after CABG is contraindicated according to the Food and Drug Administration recommendations because it has a similar mechanism of action such as valdecoxib and parecoxib.

Cardiac surgery is a highly invasive surgery due to thoracotomy and the use of cardiopulmonary bypass (CPB). Tissue injury with cardiac surgery generally results in hypercoagulability related to CPB use, as demonstrated by several in vitro studies [12–15]. Therefore, patients who undergo cardiac surgery are at high risk for CV events. Currently, whether patients undergoing cardiac surgeries with CPB other than CABG are exposed to an increased risk of CV events with the short-term use of celecoxib remains unclear.

We hypothesized that short-term administration of celecoxib increases the incidence of CV adverse events in patients undergoing cardiac surgery with CPB other than CABG surgery. We aimed to determine whether short-term prescription of celecoxib increases CV events in patients after cardiac surgery with CPB compared to acetaminophen, an analgesic commonly believed to be safe for CV disease.

METHODS

This retrospective observational study was approved by the Ethics Committee of the Kyoto University Graduate School and Faculty of Medicine (approval number R0771). Informed consent was waived because of the anonymous nature of the data.

DATA SOURCE

This study included patients from the Diagnostic Procedure Combination/Per Diem Payment system in Japan. The dataset was provided by Medical Data Vision Co., Ltd (Tokyo, Japan) [16]. The Medical Data Vision database covers 13.6 million patients, 45% of all Diagnostic Procedure Combination hospitals, and represents 35% of acute-care beds in Japan. It comprises general hospitals and is not a specific geographical hospital group. This database contains patient demographic information, inpatient medical claims data, clinical diagnoses coded under the International Classification of Diseases 10th revision (ICD-10), Japan-specific standard disease codes, drug prescriptions information coded according to the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification, and health-care procedures defined using Japan-specific standardized procedure codes (K codes). Yamana et al. [17] reviewed the charts of 315 patients in geographically distant acute hospitals across Japan and concluded that the validity of Diagnostic Procedure Combination data is generally high, supporting its use in other studies.

STUDY POPULATION

This study included adult patients (≥20 years) who underwent cardiac surgery other than CABG with CPB between April 1, 2008 and March 31, 2016. Patients were classified into two groups according to the analgesics prescribed from postoperative days 0 (POD0) to 30 (POD30). Patients who used analgesics other than celecoxib or oral acetaminophen (e.g., intravenous or oral nonsteroidal anti-inflammatory drugs, and intravenous acetaminophen) were excluded. The exposure group included patients who were prescribed celecoxib at least once, whereas the control group included those who were prescribed acetaminophen at least once, without celecoxib. Patients with overlapping celecoxib and acetaminophen prescription periods were included into the celecoxib group. Patients who had been prescribed celecoxib

preoperatively were excluded because of the potential increase in CV events associated with long-term use. The types and procedural codes for cardiac surgery used in this study are listed in **Supplementary Table 1**. Cardiac surgery, CPB, and the prescribed drugs were identified using procedural or ATC codes. The first date of celecoxib or acetaminophen administration after cardiac surgery was defined as the index date, and outcomes were assessed within 30 days after the first postoperative prescription of celecoxib or acetaminophen. Patients discharged from the hospital were difficult to follow in this database and were counted as censored cases in the Cox regression analysis. We excluded post-CABG patients because of the potential increase in CV events indicated by the previous study [11].

STUDY VARIABLES

The demographic data collected were age, sex, and hospital information. Comorbidities (defined as pre-existing conditions before or at admission) included CAD, congestive heart failure, ischemic stroke, chronic obstructive pulmonary disease, chronic kidney disease, diabetes mellitus, liver disease, and venous thrombosis, and were identified by ICD-10 codes (**Supplementary Table 2**). Some comorbidities were extracted as components of the Charlson comorbidity index using ICD-10 codes from algorithms developed by Quan et al. [18]. In the Diagnostic Procedure Combination system, conditions that occur after admission are recorded as complications, along with their index date. This system allows us to differentiate between events occurring before and after hospitalization. Procedure-related variables included surgery type (surgery for thoracic aortic aneurysm, valve surgery, or other cardiac surgeries); duration of CPB (in minutes); and the use of red blood cell transfusion, extracorporeal membrane oxygenation, and intra-aortic balloon pumping associated with cardiac surgeries. Medications used during the perioperative period, including dopamine, dobutamine, norepinephrine, anticoagulants, and antiplatelet drugs, were estimated from the ATC codes. Hospital information included the hospital type (training or non-training) and volume. The hospital volume of cardiac surgeries per year with CPB was classified into 10 categories, to adjust for differences in surgical outcomes among hospitals derived from the number of operations. The remaining variables included the days from hospitalization to surgery and the days from surgery to the first administration of celecoxib or acetaminophen.

OUTCOME DEFINITION

The primary clinical outcomes were all-cause death and CV events, defined as CAD, ischemic stroke, pulmonary embolism, and venous thrombosis coded using ICD-10 (**Supplementary Table 2**) within 30 days after the first postoperative prescription of celecoxib or acetaminophen. The secondary outcome was the postoperative length of stay.

STATISTICAL ANALYSIS

Data were presented as mean and standard deviation for normally distributed continuous variables, median (25th and 75th percentiles) for skewed data, and proportions for categorical variables. Patients with incomplete data regarding the index procedure were excluded. We used a multivariable logistic regression model to estimate a propensity score (PS) based on the potential confounders between exposure to drug and outcome, which were selected on the basis of our clinical knowledge (**Table 1**). A caliper was fixed at 0.2 standard deviation of the log odds of the PS. We performed nearest neighbor matching using PS estimates to balance the covariates and control selection bias between the two groups. The analyses were adjusted for the baseline characteristics listed in **Table 1**. An absolute standardized mean difference of >10% indicates a meaningful imbalance [19]. Variables with a standardized mean difference of >10% after matching, underwent multivariate Cox regression analysis to account for residual imbalance. For time-to-event analyses, we obtained Kaplan-Meier estimates and tested the equality of the survival curves using the log-rank test. We also calculated the statistical power before and after PS matching for the interpretation of results. Statistical significance was set at $P < 0.05$, and all statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

SENSITIVITY ANALYSES

To increase the patient homogeneity, we performed a sensitivity analysis that only included patients who were prescribed analgesics within 3 days after surgery.

PATIENT AND PUBLIC INVOLVEMENT

Patient or public were not involved in the design development or implementation of this study.

RESULTS

BASELINE

Of the 16,141 patients who underwent cardiac surgery

Table 1 Patient demographics

	Full cohort			Matched cohort		
	Celecoxib (n = 904)	Acetaminophen (n = 5,002)	SMD (%)	Celecoxib (n = 885)	Acetaminophen (n = 885)	SMD (%)
Age (years)	66 ± 13.1	69 ± 12.4	24.6	67 ± 12.9	67 ± 13.3	4.9
Male	562 (62.2)	2,969 (59.4)	5.8	551 (62.3)	531 (60.0)	4.6
Comorbidities						
Coronary artery disease	136 (15.0)	1,032 (20.6)	14.6	135 (15.3)	171 (19.3)	10.8
Cerebral infarction	29 (3.2)	227 (4.5)	6.9	28 (3.2)	34 (3.8)	3.7
Heart failure	298 (33.0)	1,706 (34.1)	2.4	291 (32.9)	293 (33.1)	0.5
Deep venous thrombosis	6 (0.7)	49 (1.0)	3.5	6 (0.7)	6 (0.7)	0.0
Hepatic failure	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	0.0
Diabetes	118 (13.1)	887 (17.7)	13.0	115 (13.0)	117 (13.2)	0.7
COPD	23 (2.5)	119 (2.4)	1.1	23 (2.6)	30 (3.4)	4.6
Renal failure	52 (5.8)	492 (9.8)	15.3	52 (5.9)	62 (7.0)	4.6
Mechanical ventilation[a]	10 (1.1)	79 (1.6)	4.1	10 (1.1)	10 (1.1)	0.0
Medications						
Dopamine[b]	461 (51.0)	2,567 (51.3)	0.6	448 (50.6)	467 (52.8)	4.3
Dobutamine[b]	537 (59.4)	3,099 (62.0)	5.2	534 (60.3)	516 (58.3)	4.1
Norepinephrine[b]	667 (73.8)	3,736 (74.7)	2.1	649 (73.3)	629 (71.1)	5.1
Anticoagulants[b]	494 (54.6)	3,077 (61.5)	14.0	485 (54.8)	485 (54.8)	0.0
Antiplatelet agents[b]	318 (35.2)	2,161 (43.2)	16.5	314 (35.5)	321 (36.3)	1.6
Emergency	209 (23.1)	1,415 (28.3)	11.8	208 (23.5)	196 (22.1)	3.2
Re-operation	65 (7.2)	310 (6.2)	4.0	64 (7.2)	68 (7.7)	1.7
Median CPB time (min)	190	197	0.2	192	200	4.3
Transfusion	747 (82.6)	4,251 (85.0)	6.4	740 (83.6)	752 (85.0)	3.7
IABP[a]	27 (3.0)	145 (2.9)	0.5	27 (3.1)	26 (2.9)	0.7
ECMO[a]	2 (0.2)	25 (0.5)	3.2	2 (0.2)	1 (0.1)	2.8
Operation type			7.8			1.1
thoracic aortic surgery	462 (51.1)	2,392 (47.8)		459 (51.9)	458 (51.8)	
Valve surgery	403 (44.6)	2,421 (48.4)		391 (44.2)	390 (44.1)	
Others	39 (4.3)	188 (3.8)		35 (4.0)	37 (4.2)	
Median POPD	2	4	15.8	2	3	8.5
Median POD	2	3	13.5	2	3	4.4
Hospital information						
Cardiac surgical volume per year			96.6			18.8
0–99	180 (19.9)	1,018 (20.4)		184 (20.8)	217 (24.5)	
100–199	388 (42.9)	1,280 (25.6)		369 (41.7)	311 (35.1)	
200–299	127 (14.0)	1,151 (23.0)		127 (14.4)	139 (15.7)	
300+	205 (22.7)	1,295 (25.9)		205 (23.2)	218 (24.6)	
Training hospital	710 (78.5)	3,716 (74.3)	10.0	699 (79.0)	679 (76.7)	5.4

Data are presented as n (%), except age and CPB time, which are presented as mean ± standard deviation and median, respectively.
[a]Preoperative use. [b]Intraoperative or postoperative use.
SMD, standardized mean difference; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; IABP, intra-aortic balloon pumping; ECMO, extracorporeal membrane oxygenation; POPD, postoperative prescribed day; POD, preoperative day

with CPB during the study period, 11,199 patients were eligible for the study. Among these, 904 patients received celecoxib and 5,002 received acetaminophen from POD0 to POD30 (total: 5,906 patients). The median time to prescription after surgery was 3 days for the celecoxib group and 2 days for the acetaminophen group. The average follow-up after oral analgesic prescription was 22.7 days and 25.1 days in the celecoxib and acetaminophen groups, respectively. The number of patients after PS matching was 885 in each group (**Fig. 1**). The patient, hospital, and surgical characteristics of the study cohort before and after PS matching are presented in **Table 1**. The baseline characteristics between the two groups were balanced after PS matching except for coronary artery disease and cardiac surgical volume distribution.

OUTCOME ANALYSIS

Before PS matching, 154 (2.6%) patients experienced CV events or died (celecoxib group, 11 [1.2%]; acetaminophen group, 143 [2.9%]). Differences in the risk of the combined end point between the celecoxib and acetaminophen groups were significant (hazard ratio, 0.46; 95% confidence interval, 0.25–0.85).

After PS matching and multivariate Cox regression, the administration of celecoxib after cardiac surgery was not associated with an increase in the number of CV events or deaths compared with acetaminophen (hazard ratio, 0.76; 95% confidence interval, 0.35–1.65) (**Table 2**). The cumulative curve illustrates the incident rate of CV events or death in the first 30 days after prescribing celecoxib or acetaminophen (**Fig. 2**). When a 30-day follow-up was performed after prescribing analgesic drugs, there was no statistical difference between the two groups regarding the incidence of the combined end points (log-rank test; $P = 0.53$) (**Fig. 2**).

The median postoperative length of stay was shorter in the celecoxib group than in the acetaminophen group ($P < 0.001$) (**Table 2**).

SENSITIVITY ANALYSIS

The number of patients who were prescribed analgesics within 3 postoperative days after PS matching was 508 in each group. Similar to the primary analysis, the incidence of CV events or death in the celecoxib group did not significantly increase (hazard ratio, 0.51; 95% confidence interval, 0.17–1.48).

DISCUSSION

We assessed whether celecoxib administration in the postoperative period increased the frequency of CV events compared to acetaminophen. There was no statistical difference between the two groups regarding the incidence of CV events and death after PS matching and

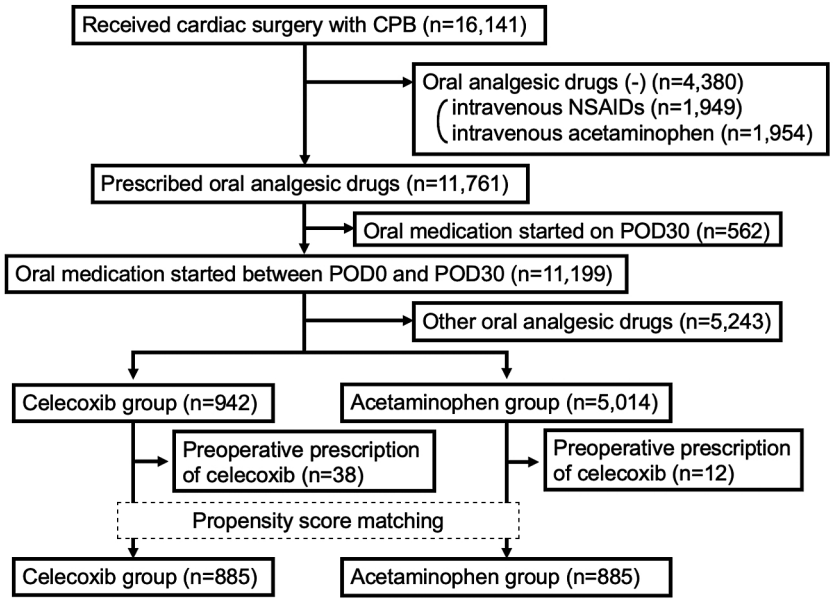

Fig. 1 Flowchart depicting enrolment into the study cohort

Cardiac surgery includes all cardiac surgeries other than coronary artery bypass grafting. CPB, cardiopulmonary bypass; POD, postoperative day.

Table 2 Patient outcomes

	Celecoxib (n = 885)	Acetaminophen (n = 885)	Total (n = 1,770)	HR (95% confidence interval)
CV events	4 (0.5)	8 (0.9)	12 (0.7)	0.53 (0.16–1.74)
CAD	1 (0.1)	0 (0.0)	1 (0.1)	NA
CI	2 (0.2)	6 (1.0)	8 (0.5)	0.35 (0.70–1.71)
PE	1 (0.1)	1 (0.1)	2 (0.1)	1.00 (0.06–16.0)
DVT	0 (0.0)	1 (0.1)	1 (0.1)	NA
Death	7 (0.8)	7 (0.8)	14 (0.8)	1.08 (0.38–3.07)
All events	11 (1.2)	15 (1.7)	26 (1.5)	0.76 (0.36–1.70)
Postoperative length of stay (days)	23 (17–33)	26 (19–39)	24 (18–35)	

Data are presented as n (%), except for postoperative length of stay, which is presented as median (interquartile range).
HR, hazard ratio; CV, cardiovascular; CAD, coronary artery disease; CI, cerebral infarction; PE, pulmonary embolism; DVT, deep vein thrombosis; NA, not applicable.

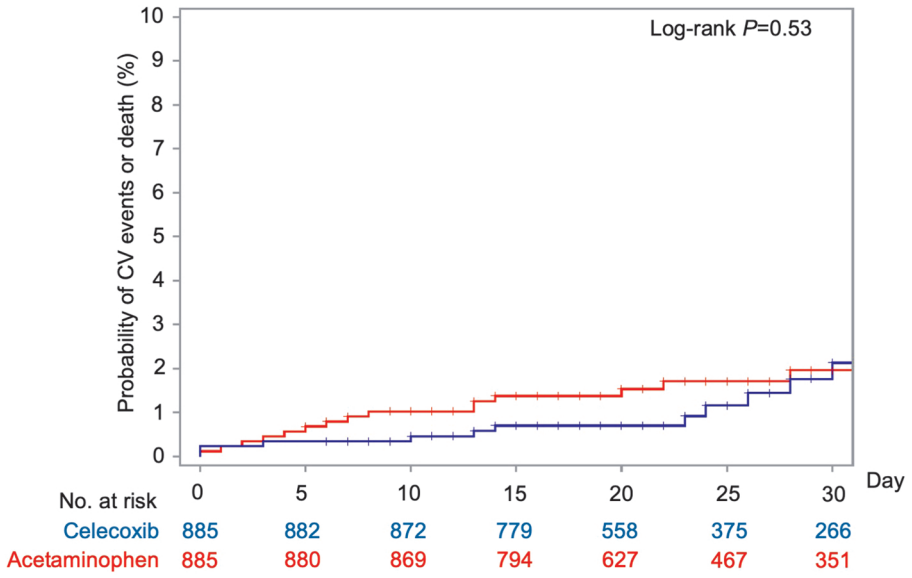

Fig. 2 Cumulative incidence rate curves for the primary composite outcome (cardiovascular [CV] events or death) according to group

multivariate Cox regression.

Previous studies have shown that celecoxib was substantially safer in that it did not increase the frequency of CV events with short-term use in patients after undergoing percutaneous coronary intervention or in outpatients of veterans [20, 21]. Several mechanisms have been described; celecoxib may reduce the viability of vascular smooth muscle cells, suppress the growth of neointima, and/or decrease the rate of revascularization [20]. The potentiation of the nitric oxide synthase/pathway by celecoxib possibly counteracts any potential detrimental increase in vasoconstriction [22]. In addition, the short-term use of celecoxib does not necessarily increase the risk of CV events in vitro. Our results agree with these previous in-vitro studies, but the mechanism or causality of the protective effect of short-term celecoxib use,

remains to be elucidated.

Although we estimated from previous studies that CV events and all-cause death occurred at a rate of at least 10% [23–25], we observed a rate of 2.0%. In the present study, we included only patients who could take oral medicine; these patients are thought to be in better condition than those on parenteral medications. As the number of events was less than expected, we did a post-hoc statistical power calculation. A reasonable value for power was at least 0.8; the statistical power after PS matching was 0.12. As the statistical power was underpowered in all other outcomes (e.g., CAD, cerebral infarction, death), our study may have missed the small but important difference for each of the outcomes.

This study had several limitations. First, the database does not include detailed information on factors relevant to a patients' outcome, such as disease severity at the patient level (e.g., the Sequential Organ Failure Assessment score [26], operation time, surgical blood loss), surgical techniques of the operator at the physician level, and institutional variations of quality of care at the hospital level. Therefore, we could not detect the exact difference in severity or hospitals' surgical performance. Nevertheless, the difference in severity may be small because the analyses were adjusted between the two groups for the components of the Charlson comorbidity index, CPB time, and hospital information to address this limitation (**Table 1**). Second, specifying the actual dosage taken by the patients was impossible; however, the prescribed dose could be specified. We were unable to investigate a dose-dependent relationship of celecoxib or acetaminophen using this database. Third, follow-up evaluations of discharged patients were difficult, and it was impossible to identify the event occurrence of discharged patients. To adequately deal with this situation, we handled such patients as censored cases in the Cox regression analysis. In addition, the median follow-up durations were 22.7 days and 25.1 days in the celecoxib and acetaminophen groups, respectively. The interval between discharge and POD30 was relatively short, and the CV risk after discharge was expected to be low. These minimized the effects of observation biases. Fourth, there may be heterogeneity within the target population due to differences in the timing of analgesic prescription. We performed a sensitivity analysis on patients prescribed within 3 days after surgery. Results of sensitivity analysis were consistent with main analysis. The effect of heterogeneity was considered small. Finally, the diagnosis of CV events was based on the diagnostic codes registered by the physicians. Our primary outcome was considered as a severe outcome. In our claims data, this has a relatively high specificity and high positive predictive value [17, 27, 28]. Therefore, the possibility of a discrepancy between the actual states and coding may be small.

CONCLUSION

The prescription of celecoxib in patients who had undergone cardiac surgery with CPB was not statistically different from the prescription of acetaminophen in the incidence of CV events and death. Although further investigations are needed, celecoxib may be a candidate for multimodal analgesia in patients receiving cardiac surgery in the era of opioid epidemics.

CONFLICT OF INTERESTS

KK received honoraria from Shin Nippon Biomedical Laboratories; research funds from Bayer Yakuhin, CMIC, Novartis Pharma K.K., Suntory Beverage & Food, Dainippon Sumitomo Pharma and Stella Pharma; and holds stocks in School Health Record Center and Real-World Data. There are no patent products under development or marketed products to declare, relevant to these companies.

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