Efficacy and Safety of the Selective Cyclooxygenase-2 Inhibitor Celecoxib in the Treatment of Rheumatoid Arthritis and Osteoarthritis in Japan

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Key Words

Celecoxib • COX-2 inhibitor, selective • Gastrointestinal disorders • Cardiovascular disorders

Abstract

Background/Aims: Gastrointestinal (GI) disorders are common adverse reactions of nonsteroidal anti-inflammatory drugs (NSAIDs). Loxoprofen is a representative NSAID widely used in East Asia. A selective cyclooxygenase-2 inhibitor, celecoxib, was introduced in Japan in 2007. In this study, we aimed to compare the efficacy and safety of celecoxib with those of loxoprofen in Japanese patients. **Methods:** We analyzed the data from 12 clinical studies conducted in Japan. These data of Japanese patients were compared with those of the patients in the West that had been published after 2000. **Results:** The efficacy of celecoxib as an analgesic was comparable to that of loxoprofen, whereas serious GI events, including symptomatic ulcers, were significantly less frequent with celecoxib than with loxoprofen in Japanese patients with rheumatoid arthritis (RA) and osteoarthritis (OA) ($p = 0.039$). These results were consistent with the findings of the studies conducted in the West. The incidence of serious cardiovascular events was 0.1% in 2,398 subjects on celecoxib, which was not statistically different from the inci-

dence in subjects on loxoprofen (0.3%; $p = 0.3404$) and those on placebo (0.2%); this result was also consistent with the data of the studies conducted in the West. **Conclusion:** The analgesic activity of celecoxib, which was used for the treatment of RA, OA, and low back pain, was comparable to that of loxoprofen, and celecoxib was safer in terms of GI injury often caused by other nonselective NSAIDs.

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) exert anti-inflammatory and analgesic effects by inhibiting cyclooxygenase (COX) activity in the arachidonic acid cascade, and thus inhibit prostaglandin (PG) synthesis [1]. In the 1990s, 2 COX isoenzymes – COX-1 and COX-2 – were identified [2, 3]. It is now well known that COX-1 is expressed constitutively in a variety of tissues and is involved in PG synthesis under normal physiological conditions in which PG protects the gastric mucosa and maintains renal and platelet functions [4, 5]. In contrast, COX-2 has been shown to be induced in inflamed tissues and is involved in PG synthesis associated with inflammation [6, 7]. Thus, conventional NSAIDs that inhibit

both COX-1 and COX-2 to varying degrees exert therapeutic effects by inhibiting COX-2. The adverse effects of NSAIDs, particularly in the upper gastrointestinal (GI) tract, are considered to be mainly caused by the inhibition of COX-1 activity, which is involved in gastric mucosal protection [8, 9]. GI injury associated with NSAIDs is a serious clinical problem since NSAID-related ulcer complications have been estimated to lead to 10,000 cases of hospitalization and 16,500 deaths yearly in the United States [10]. Therefore, attempts were made to develop drugs targeted against COX-2 to reduce adverse reactions to NSAIDs, while retaining their anti-inflammatory and analgesic actions. In 1998, celecoxib was approved as the first selective COX-2 inhibitor [11]. Celecoxib is a member of the coxib family, which is a drug family included in the anatomical therapeutic chemical (ATC) classification system; it is characterized by a 3-dimensional structure of molecules designed to afford COX-2 selectivity [11]. Celecoxib has been available in Japan since June 2007 and is indicated for rheumatoid arthritis (RA), osteoarthritis (OA), and inflammation and pain associated with RA or OA.

Despite cases of serious NSAID-related ulcer complications in the United States [10], few studies have reported NSAID-related upper GI injuries in Japan where the main cause of gastroduodenal ulcers is *Helicobacter pylori*; the prevalence of infection with *H. pylori* in Japan is much higher than in the United States [12]. In addition, the types and doses of NSAIDs used for the treatment of patients with RA or OA in Japan are very different from those used in the United States. For example, the maximum prescribed dose of diclofenac in Japan is 100 mg/day, whereas in the United States it is 200 mg/day. Furthermore, the most frequently prescribed NSAID in Japan is loxoprofen, which is a prodrug that is marketed only in Asia, Mexico, and Brazil, but not in the United States. The lower number of studies on the adverse effects of NSAIDs on gastroduodenal mucosa in Japan can be attributed to differences with regard to upper GI injury and its treatment in Japan and the United States. Therefore, it seems important for us to make it clear how the NSAIDs we usually use are safe or harmful in terms of drug-related gastroduodenal injury.

The aim of this study was to review the clinical efficacy and safety data of celecoxib in comparison with those of loxoprofen, which is a widely used form of propionic acid in East Asia, in Japanese trials and to inform doctors about the efficacy and safety of NSAIDs in Japanese patients with RA or OA.

Clinical Efficacy of Celecoxib

Clinical Efficacy in RA Treatment

Twelve phase II and III clinical trials of celecoxib, including 2 placebo-controlled double-blind trials, 2 double-blind loxoprofen-controlled celecoxib trials, and 1 double-blind placebo- and loxoprofen-controlled celecoxib trial, were conducted in Japan to evaluate the efficacy and safety of celecoxib in the treatment of patients with RA, OA, and low back pain (table 1). In these trials, a total of 2,410 patients received celecoxib, 1,190 patients loxoprofen, and 414 patients placebo [13–22]. The details of the trials are summarized in table 1. The efficacy and safety of celecoxib in the treatment of patients with RA were examined in 4 trials, including a double-blind trial including 771 patients with RA to compare the efficacy and safety of 12 weeks' treatment with celecoxib (200 mg b.i.d.) with those of loxoprofen (60 mg t.i.d.) (table 1) [14]. In this trial, celecoxib was comparable to loxoprofen sodium in the evaluation of both final 'improvement rate' as a primary endpoint and 'time course of percent improvement' according to the American College of Rheumatology (ACR) Improvement Criteria (fig. 1). In 'self-assessment of pain by patients' using the visual analog scale (VAS), the scores revealed that the levels of improvement in patients in the celecoxib treatment group at 2 and 4 weeks after the start of treatment were significantly higher than the corresponding levels in patients in the loxoprofen sodium treatment group, thereby indicating that more rapid improvement can be achieved with celecoxib (fig. 2). These data are consistent with those of a previously published overseas study in which the efficacy of celecoxib (200 mg b.i.d.) in the treatment of patients with RA was compared to that of diclofenac SR (75 mg b.i.d.) [23].

These results showed that the efficacy of celecoxib in the treatment of patients with RA is comparable to that of conventional RA drugs such as loxoprofen sodium and diclofenac.

Clinical Efficacy in OA Treatment

The efficacy and safety of celecoxib in the treatment of patients with OA were also examined in 4 trials, including a double-blind trial, in 949 patients with OA to compare the efficacy and safety of 4 weeks' treatment with celecoxib (100 mg b.i.d.) with those of loxoprofen (60 mg t.i.d.) or placebo (table 1) [17]. In this double-blind trial, with regard to the rate of improvement in the final global improvement assessment (the primary endpoint), the level of improvement in the patients in the celecoxib group

Table 1. List of 12 clinical trials conducted in Japan to evaluate the efficacy and safety of celecoxib in patients with RA, OA, and low back pain

Authors/ year of publication	Disease entity	Study design	Pa- tients n	Facili- ties n	Drug dose	Patients who received/completed/ discontinued therapy n	Term weeks	Outcome and method of evaluation
Abe et al. [13]/2006	RA	Open	54	18	Celecoxib 50 mg b.i.d. Celecoxib 100 mg b.i.d. Celecoxib 200 mg b.i.d.	19/11/8 17/14/3 18/11/7	6	Determination of the rate of improvement/self-assessment using VAS or on the basis of adverse effects
Abe et al. [13]/2006	RA	Randomized double-blind placebo-controlled	423	112	Celecoxib 25 mg b.i.d. Celecoxib 100 mg b.i.d. Celecoxib 200 mg b.i.d. Placebo b.i.d.	98/83/15 89/83/6 92/83/9 95/75/20	4	Determination of the rate of improvement on the basis of ACR improvement criteria/self-assessment using VAS or on the basis of adverse effects
Abe et al. [14]/2006	RA	Randomized double-blind comparison of celecoxib with loxoprofen	831	195	Celecoxib 200 mg b.i.d. Loxoprofen 60 mg t.i.d.	382/319/63 389/326/63	12	Determination of the rate of improvement on the basis of ACR improvement criteria/self-assessment using VAS or on the basis of adverse effects, including GI events
Azuma [15]/2006	RA	Open	156	13	Celecoxib 200–400 mg b.i.d.	200 mg: 111/78/33 400 mg: 45/35/10	52	Determination of the rate of improvement on the basis of ACR improvement criteria/self-assessment using VAS or on the basis of adverse effects
Aoki et al. [16]/2006	OA	Open	65	22	Celecoxib 25 mg b.i.d. Celecoxib 50 mg b.i.d. Celecoxib 100 mg b.i.d.	20/16/4 23/17/6 18/15/3	4	Determination of the rate of improvement/adverse effects
Aoki et al. [16]/2006	OA	Randomized double-blind placebo-controlled	518	89	Celecoxib 25 mg b.i.d. Celecoxib 50 mg b.i.d. Celecoxib 100 mg b.i.d. Placebo b.i.d.	129/115/14 125/108/17 118/103/15 127/110/17	4	Determination of the rate of improvement/adverse effects
Sugawara [17]/2006	OA	Randomized double-blind place- bo-controlled com- parison of celecoxib with loxoprofen	959	85	Celecoxib 100 mg b.i.d. Loxoprofen 60 mg t.i.d. Placebo t.i.d.	377/342/35 380/345/35 192/177/15	4	Determination of the rate of improvement/self-assessment using VAS/ WOMAC OA index or on the basis of adverse effects, including GI events
Sugawara [18]/2006	OA	Open	65	4	Celecoxib 100–200 mg b.i.d.	100 mg: 55/40/15 200 mg: 10/8/2	28–52	Self-assessment using VAS or on the basis of adverse effects
Kikuchi et al. [19]/2009	Low back pain	Randomized double-blind comparison of celecoxib with loxoprofen	881	80	Celecoxib 100 mg b.i.d. Loxoprofen 60 mg t.i.d.	425/400/25 421/390/31	4	Improvement rate/self-assessment using VAS or on the basis of adverse effects, including GI events
Takagishi [20]/2009	Periar- thritis of the shoulder	Open	81	13	Celecoxib 100 mg b.i.d.	77/70/7	4	Improvement rate/self-assessment using VAS or on the basis of adverse effects
Takagishi [21]/2009	Cervico- omo- brachial syndrome	Open	85	13	Celecoxib 100 mg b.i.d.	82/78/4	4	Improvement rate/self-assessment using VAS or on the basis of adverse effects
Ogino [22]/2009	Tenosy- novitis	Open	80	11	Celecoxib 100 mg b.i.d.	80/76/4	2	Improvement rate/self-assessment using VAS or on the basis of adverse effects

A search of the Japan Medical Abstract Service ICHUSHI was performed to find clinical trials that compared the efficacy and safety of celecoxib with those of loxoprofen; we found 12 trials. All trials were different from each other in terms of the design, disease entity studied, drug administration, etc. All original articles were written in Japanese.

Fig. 1. Efficacies of celecoxib and loxoprofen sodium in patients with RA in a clinical trial conducted in Japan [14]. A total of 771 patients with RA were randomly administered 12-week oral treatment with celecoxib (200 mg b.i.d.) or loxoprofen sodium (60 mg t.i.d.). The efficacy of celecoxib in terms of the rate of improvement in the patients was compared with that of loxoprofen. The rate of improvement was determined on the basis of the ACR improvement criteria [98].

was significantly higher than that in the patients in the placebo group and was comparable to that in the patients in the loxoprofen sodium group (fig. 3). In addition to the assessment of pain using the VAS, the patients were assessed by the composite OA index (pain, stiffness, and physical function) developed by the Western Ontario McMaster Universities (WOMAC) (secondary endpoint). The scores revealed that the level of improvement in the patients in the celecoxib group was significantly higher than that in the patients in the placebo group and was comparable to that in the patients in the loxoprofen sodium group [17].

These data are also consistent with those of an overseas study in which the efficacy of celecoxib in a 6-week treatment regimen (100 mg b.i.d.) was compared to that of diclofenac (50 mg t.i.d.) or placebo [24].

These results indicated that in patients with OA, celecoxib can alleviate symptoms to a degree comparable to that achieved with loxoprofen sodium or diclofenac.

Safety of Celecoxib

Upper GI Disorders

Peptic ulcers in Japanese patients are mainly attributed to *H. pylori* infection. NSAID is the second most common cause of peptic ulcers in Japan, where the most commonly prescribed nonselective NSAID is loxoprofen. Loxoprofen produced by Daiichi-Sankyo and marketed in Japan since 1986 is a prodrug of propionic acid derivative that is activated in the liver, and it does not cause direct adverse reaction to the gastric mucosa. In fact, a double-blind controlled study in healthy Japanese volunteers

Fig. 2. Efficacies of celecoxib and loxoprofen sodium in patients with RA in a clinical trial conducted in Japan [14]. Joint pain was self-assessed by the patients using the VAS. The efficacy of celecoxib in terms of the scores reported by 771 patients was compared with that of loxoprofen. The VAS consists of a 100-mm horizontal or vertical line with 2 endpoints labeled 'no pain' and 'worst pain ever' (or similar verbal descriptions). Mean change $\pm$ SD. * $p < 0.05$ [t test (significance level = 5%, two-tailed) vs. loxoprofen sodium group].

revealed that subjects on loxoprofen had a significantly lower rate of gastric injury than those on diclofenac [25]. Another study on 1,206 Asian patients taking loxoprofen revealed that only 0.24% patients had GI bleeding and required hospitalization [26]. Therefore, loxoprofen is considered safe as compared to other nonselective NSAIDs such as indomethacin and diclofenac. A recent survey on the prescription of nonselective NSAIDs by

Fig. 3. Efficacies of celecoxib and loxoprofen sodium in patients with OA in a clinical trial conducted in Japan [17]. A total of 949 patients with OA were randomly administered 4-week oral treatment with celecoxib (100 mg b.i.d.), loxoprofen sodium (60 mg t.i.d.), or placebo. The efficacy of celecoxib in terms of the rate of improvement in the final global improvement assessment was compared with that of loxoprofen. The rate of improvement in the final global improvement assessment is a ratio of the number of subjects that were evaluated during the final global improvement

assessment to the total number of subjects. The final global improvement assessment consists of 5 stages (stage 1 = marked improvement; stage 2 = moderate improvement; stage 3 = slight improvement; stage 4 = no change, and stage 5 = worsening of condition) based on global improvement assessment by doctors by using the VAS. Values in parentheses represent moderately or markedly improved cases. * $p < 0.05$ [Cochran-Mantel-Haenszel test (significance level = 5%, two-tailed) vs. placebo group].

physicians in East Asia [27] has shown that, overall, loxoprofen is the first choice of nonselective NSAIDs and is prescribed most frequently, followed by diclofenac.

Although there have been few reports on gastroduodenal injuries in Japanese patients taking NSAIDs, the Japan Rheumatism Foundation showed in 1991 for the first time that 62.2% of patients with RA who had taken NSAIDs for more than 3 months had gastroduodenal injuries, including ulcers and erosions [28]. This is the first comprehensive report that has revealed the prevalence of NSAID-related gastroduodenal injuries in Japanese patients with RA on NSAIDs, which has increased the concern of Japanese physicians, especially rheumatologists and gastroenterologists, about the high prevalence of NSAID-related gastroduodenal injuries. The incidence of endoscopically detected upper GI lesions, however, appears to remain unchanged during the 15-year period since the first report in 1991 [28]. A recent cross-sectional endoscopic analysis conducted in 2006 [29] has shown that 62.8% of the patients who regularly took NSAIDs had gastroduodenal injuries, even though loxoprofen was prescribed as the first choice of NSAID for long-term NSAID users. According to a recent report, the incidence of NSAID-associated gastroduodenal ulcers is higher than 20% in Japanese RA outpatients having taken

NSAIDs for 3 or more months [30]. In the recent and first epidemiological study in Japan [31], the risks of upper GI bleeding have been shown to be about 6 and 11 times higher, respectively, in subjects taking loxoprofen and diclofenac than in subjects not taking NSAIDs. Thus, the risk of upper GI bleeding for loxoprofen users was identified for the first time in this study. The striking finding of this study is that the odds ratio of loxoprofen was consistent with those of all other NSAIDs reported in case-control studies published in Western Europe since 2000 [32–42] (table 2). All these recent data suggest that NSAIDs, especially loxoprofen, which accounted for 87% of all NSAID prescriptions in Japan, is a cause of concern in terms of the treatment-associated gastroduodenal injuries.

Thus, the safety of celecoxib and loxoprofen in terms of GI injury was compared in 3 trials before celecoxib was approved by the government in Japan (table 1) [14, 17, 19]. The GI adverse effects observed in these 3 trials were combined and analyzed in 1,184 RA, OA, and low back pain patients taking celecoxib and 1,190 patients taking loxoprofen [43]. The results of this analysis indicated that the incidence of symptomatic gastroduodenal ulcers and hemorrhagic events (serious GI events) was significantly lower in the celecoxib 100–200 mg b.i.d. group (0.1%) than

Table 2. Odds ratio or relative risk of upper GI bleeding in users of NSAIDs or individual NSAIDs

Authors/year of publication	Country	Study design and number of cases	Odds ratio (OR) or Relative risk (RR)	Adjusted for medications
Hernández-Díaz and Rodríguez[32]/2000	–	Overview of 18 case-control studies published between 1990 and 1999 Total number of cases: 12,552; total number of controls: 64,871	Pooled RR = 3.8	–
Stack et al. [33]/2002	UK	Cases: 203; controls: 203	OR = 10.6	–
Ofman et al. [34]/2002	–	16 RCT 23 case-control studies 9 cohort studies	Pooled OR of 16 RCTs = 5.36 Pooled OR of 23 case-control studies = 3.0 Pooled RR of 9 cohort studies = 2.7	–
Lewis et al. [35]/2002	–	Meta-analysis of 3 case-control studies Cases: 2,472; controls: 5,877	Ibuprofen: OR = 1.7; diclofenac: OR = 4.9; indomethacin: OR = 6.0; naproxen: OR = 9.1; piroxicam: OR = 13.1; ketoprofen: OR = 34.9	–
Laporte et al. [36]/2004	Spain, Italy	Case-control study Cases: 2,813; controls: 7,193	Ketorolac: OR = 24.7; aceclofenac: OR = 1.4; celecoxib: OR = 0.3; dexketoprofen: OR = 4.9; meloxicam: OR = 5.7; nimesulide: OR = 3.2; rofecoxib: OR = 7.2	PPI, H2RA
Nørgård et al. [37]/2004	Denmark	Case-control study Cases: 780; controls: 2,906	NSAIDs: OR = 3.3; celecoxib: OR = 1.3; rofecoxib: OR = 2.1	PPI, H2RA
Tata et al. [38]/2005	UK	Case-control study Cases: 11,261; controls: 53,156	NSAIDs: OR = 2.15	–
Hippisley-Cox et al. [39]/2005	UK	Nested case-control study Cases: 9,407; controls: 88,867	Naproxen: OR = 2.12; diclofenac: OR = 1.96; rofecoxib: OR = 1.56; celecoxib: OR = 1.11	–
Lanas et al. [40]/2006	Spain	Cases-control study Cases: 2,777; controls: 5,532	NSAIDs: RR = 5.3; aceclofenac: RR = 3.1; ketorolac: RR = 14.4; rofecoxib: RR = 2.1; celecoxib: RR = 1.0	No adjustment Present PPI users: RR = 0.62 Past PPI users: RR = 1.53 Present H2RA users: RR = 1.31 Past H2RA users: RR = 1.74
García Rodríguez et al. [41]/2007	UK	Nested case-control study Cases: 1,561; controls: 10,000	NSAIDs: RR = 3.7; coxibs: RR = 2.6	Gastroprotectives
Helin-Salmivaara et al. [42]/2007	Finland	Case-control study Cases: 9,191; controls: 41,780	Meloxicam: OR = 3.09; naproxen: OR = 2.61; ibuprofen: OR = 1.58; diclofenac: OR = 3.22; celecoxib: OR = 1.77; rofecoxib: OR = 2.66	PPI, H2RA
Sakamoto et al. [31]/2006	Japan	Case-control study Cases: 175; controls: 347	NSAIDs: OR = 6.1; diclofenac: OR = 10.9; loxoprofen: OR = 5.5	–

A Medline search for articles published between 2000 and 2008 was performed to search for the terms ‘nonsteroidal anti-inflammatory drugs’ and ‘risk of GI bleeding’. The search was restricted to studies in adult humans and case-control studies or meta-analysis of case-control studies. RCT = Randomized-controlled trial.

in the loxoprofen sodium 60 mg t.i.d. group (0.7%; $p = 0.039$) (table 3). This analysis was the first attempt to compare the frequency of serious GI event in subjects taking celecoxib and loxoprofen. With regard to the serious upper GI events, including symptomatic gastroduodenal ulcers and hemorrhagic events, celecoxib was safer than loxoprofen. However, the incidence of endoscopically confirmed gastroduodenal ulcers remains to be compared between subjects taking celecoxib and loxoprofen.

Thus far, many studies in the West have compared the safety of celecoxib to that of other NSAIDs such as diclofenac, ibuprofen, or naproxen. In these studies, the incidence of gastroduodenal ulcers and ulcer complications has been examined; the incidence of NSAID-associated gastroduodenal ulcers was confirmed by endoscopy as a surrogate marker of serious GI events (endoscopic trial) and NSAID-associated serious GI event rates including rates of symptomatic ulcers and complications of gastro-

duodenal ulcers such as upper GI bleeding, perforation, and obstruction.

In an endoscopic trial involving 1,149 patients with RA [44], the incidence of endoscopically identified gastroduodenal ulcers was lower in the celecoxib group than in the naproxen group and comparable to that in the placebo group. In another celecoxib trial [23], 655 patients with RA were randomly assigned to celecoxib or diclofenac SR for 24 weeks; gastroduodenal ulcers were endo-

scopically detected in 33 (15.1%) of 218 patients on diclofenac and 8 (3.8%) of 212 patients on celecoxib ($p < 0.001$). According to a Cochrane Collaboration systematic review, 5 [23, 44–47] endoscopic studies on 2,439 patients comparing celecoxib with nonselective NSAIDs showed a 79% reduction in the relative risk of gastroduodenal ulcers (table 4) [48].

Instead of the selective COX-2 inhibitor, celecoxib, coadministration of proton pump inhibitor (PPI) with NSAID is an alternative therapy to prevent NSAID-related gastroduodenal ulcers. Many reports have suggested that PPI is effective in preventing NSAID-related endoscopically detected gastroduodenal ulcers [49–51]. Particularly, PPI is effective in preventing the relapse of NSAID-related gastroduodenal ulcers after healing in patients in whom NSAID treatment is maintained [51]. One meta-analysis published in 2004 clearly shows that coadministration of PPI with NSAID reduces the relative risk of gastroduodenal ulcers to 0.37 as compared to that of placebo [52].

In addition to these endoscopic trials, CLASS [53] and SUCCESS-I [54] studies involving 8,059 patients with RA or OA and 13,194 patients with OA, respectively, have shown that complications, including symptomatic ulcers and hemorrhagic events, were significantly more frequent in the nonselective NSAID group as compared to those in the celecoxib group. In comparison with meloxicam, celecoxib has a 44% lower risk of perforation or

Table 3. Comparison of the incidences of symptomatic peptic ulcers and hemorrhagic events caused by celecoxib administration with those caused by loxoprofen sodium administration [43]

	Celecoxib (n = 1,184)	Loxoprofen sodium (n = 1,190)	p
Incidences of symptomatic peptic ulcers and hemorrhagic events (total cases: composition)	0.1% (1 case: gastric ulcer)	0.7% (8 cases: gastric ulcer in 4 cases, melena in 1 case, GI hemorrhage in 1 case, duodenal ulcer in 1 case, hemorrhagic gastric ulcer in 1 case)	0.039

On the basis of the data from the clinical studies conducted in Japan, the rates of the incidence of symptomatic peptic ulcers and hemorrhagic events in 2,374 patients with RA, OA, or low back pain for which a causal relationship to the drug was not ruled out were compared between the celecoxib (100–200 mg b.i.d.) group and the loxoprofen sodium (60 mg t.i.d.) group (combined analysis of data from all clinical studies in Japan).

Table 4. Comparison of the incidence of endoscopic ulcer in an RCT on celecoxib with that in RCTs on nonselective NSAIDs

Authors/year of publication	Subject	Term weeks	Ulcer incidence				
			celecoxib 100–400 mg q.d. or b.i.d.	diclofenac 75 mg b.i.d.	ibuprofen 800 mg t.i.d.	naproxen 500 mg b.i.d.	placebo
Emery et al. [23]/1999	RA, n = 655	24	200 mg b.i.d.	3.8% (8/212)	15.1% ^a (33/218)		
Simon et al. [44]/1999	RA, n = 1,149	12	100 mg b.i.d.	6.1% (9/148)		26.3%	4.0%
			200 mg b.i.d.	4.1% (6/145)		(36/137)	(4/99)
			400 mg b.i.d.	6.2% (8/130)			
Goldstein et al. [45]/2001	RA or OA, n = 537	12	200 mg b.i.d.	9%		41%	
Hawkey et al. [46]/2004	OA, n = 1,042	13	200 mg q.d.	Ulcer size >3 mm: 3.2% Ulcer size >5 mm: 2.8%	Ulcer size >3 mm: 15.7% Ulcer size >5 mm: 12.5%		
Kivitz et al. [47]/2004	RA, n = 893	13	200 mg b.i.d.	1.9%	13.6%		

Randomized control trials (RCT) comparing endoscopic ulceration of celecoxib with that of a nonselective NSAID or placebo were analyzed.

^a Diclofenac SR.

bleeding of the upper GI tract [55]. In a Cochrane Collaboration systematic review published in 2007 [48], 31,106 subjects were examined in 4 studies that assessed the effects of celecoxib and nonselective NSAIDs on serious clinical GI events (perforation, obstruction, or bleeding); the results of these studies showed that celecoxib was associated with a 77% reduction in the relative risk of serious GI events (RR 0.23; 95% CI 0.07–0.76; random effects). These data suggest that celecoxib is safer than other conventional NSAIDs, because as compared to the latter, the former has a lower incidence of endoscopically confirmed gastroduodenal ulcers and lower rates of complications, including perforation, obstruction, and bleeding. This result is very important given the current situation where the effectiveness of PPI, which has been most commonly used to prevent NSAID-associated GI injury, for the primary prevention of NSAID-associated serious GI complications is yet to be examined. Because the focus of this study was to compare celecoxib data with those of loxoprofen in Japanese RA or OA patients, it is beyond the scope of this article to comment on the effects of PPI on NSAID-related gastroduodenal ulcers and the related complications. It is well known, however, that patients with a history of upper GI bleeding are at high risk of rebleeding even if PPI is coadministered with NSAIDs or if celecoxib is used [56]. Further, celecoxib with PPIs effectively reduced the incidence of bleeding

from ulcers for 13 months in patients who had previously experienced bleeding from ulcers because of the use of NSAIDs [57]. Therefore, this combined therapy is a promising alternative for reducing the risk of upper GI disorders.

Because celecoxib has fewer adverse effects on the digestive tract, as illustrated above, the *Guidelines on Management of Peptic Ulcers in Japan*, edited by the Japanese Society of Gastroenterology [58], refer to selective COX-2 inhibitors as drugs that are endorsed as the best for preventing NSAID-associated GI injury.

Risk for Cardiovascular Disorders

As far as the cardiovascular (CV) risk is concerned, the results obtained thus far suggest that celecoxib would not cause serious adverse effects in Japanese subjects. In a combined analysis of the data of 2,410 patients on celecoxib and 1,190 patients on loxoprofen from 12 clinical studies conducted in Japan (table 1) [43], the incidence of serious CV events (0.1%) in 2,398 subjects on celecoxib 25–400 mg b.i.d. did not differ significantly from the incidence in 1,190 subjects on loxoprofen sodium 60 mg t.i.d. (0.3%; $p = 0.3404$) or placebo (0.2%) as shown in table 5. On the other hand, according to the report on the VIGOR Study in 2000 involving patients with RA or OA [59], the CV risk after treatment with another selective COX-2 inhibitor, rofecoxib (not approved in Japan), was

Table 5. Comparison of the incidence of serious CV events caused by celecoxib with those caused by loxoprofen sodium [43]

Adverse event (WHO-ART preferred terms)		Celecoxib (n = 2,398)		Loxoprofen sodium (n = 1,190)		p
		number of cases (incidence)	number of reactions	number of cases (incidence)	number of reactions	
Serious CV events		2 (0.1%)	2	3 (0.3%)	5	0.3404
CV disorder (general)	Heart failure	0	0	1 (0.1%)	1	0.0442
Myocardial, endocardial, pericardial, and valvular disorders	Angina pectoris	0	0	1 (0.1%)	1	
	Myocardial ischemia	0	0	1 (0.1%)	1	
	Myocardial infarction	0	0	1 (0.1%)	1	
Vascular (extracardiac) disorders	Cerebrovascular disease	1 (0.0%)	1	0	0	
	Cerebral bleeding	0	0	1 (0.1%)	1	
Platelet, hemorrhagic, and clotting disorders	Thrombus (thrombosis)	1 (0.0%)	1	0	0	
	Bleeding	0	0	0	0	

The incidence of serious CV events whose causal relationship to the drug was not ruled out was compared between the celecoxib (25–400 mg b.i.d.) group and the loxoprofen sodium (60 mg t.i.d.) group in 3,588 patients with RA, OA, or low back pain (com-

bined analysis of data from all clinical studies in Japan). p value: Fisher's exact test. WHO-ART = World Health Organization's Adverse Reaction Terminology.

Table 6. Risk of CV events in cohort studies on NSAIDs

Authors/year of publication	Number			Outcome evaluation	
	COX-2-selective inhibitor (celecoxib, rofecoxib, and valdecoxib) users	nonselective NSAID users	nonusers		
Solomon et al. [64]/2008	76,082	53,014	46,558	Hazard ratio	Myocardial infarction, stroke, congestive heart failure, due to a CV event 6 months before the evaluation
Haag et al. [65]/2008	7,636			Hazard ratio	Stroke
Rahme et al. [66]/2007	137,799	260,931	0	Hazard ratio	Hospitalization for acute myocardial infarction
Motsko et al. [67]/2006	2,096	10,092	0	Hazard ratio	Acute myocardial infarction, death due to coronary heart disease, cerebrovascular event
Huang et al. [68]/2006	5,312	4,290	0	Hazard ratio	Acute myocardial infarction Angina Stroke Transient ischemic attack
Hudson et al. [69]/2005	1,586	280	0	Hazard ratio	Death, recurrent congestive heart failure
Solomon et al. [70]/2006	47,393	27,445	23,532	Rate ratio	Myocardial infarction Stroke
Mamdani et al. [71]/2004	33,491	11,606	100,000	Rate ratio	Congestive heart failure
Mamdani et al. [72]/2003	27,427	39,537	100,000	Rate ratio	Acute myocardial infarction
Ray et al. [73]/2002	181,441		181,441	Rate ratio	Acute myocardial infarction, death due to coronary heart disease
Ray et al. [74]/2002	46,469	129,391	202,916	Incidence rate ratios	Acute myocardial infarction, fatal coronary heart disease
Warner et al. [75]/2008	5,825	41,932	0	Odds ratio	Acute myocardial infarction
Schneeweiss et al. [76]/2006	32,074	17,637	0	Risk differences	Acute myocardial infarction (hospitalization in the first or second position, hospital stay of at least 4–180 days)

A Medline search of articles published between 1999 and 2009 was performed to search for the terms ‘nonsteroidal anti-inflammatory drugs’, ‘cardiovascular risk’, and ‘epidemiology’. The search was restricted to studies on adult humans and case-control studies. Values in parentheses represent 95% confidence intervals.

^a Acetaminophen. ^b Etodolac. ^c Valdecoxib. ^d Diflunisal, etodolac, fenoprofen, flurbiprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, meloxicam, nabumetone, oxaprozin, piroxicam, sulindac, and tolmetin. ^e Diclofenac plus misoprostol, naproxen, ibuprofen, or diclofenac. ^f Nonnaproxen nonselective NSAIDs.

2.4 times higher than the CV risk after treatment with naproxen.

In a subsequent study on the prevention of colorectal polyp recurrence (the APPROVe Trial [60]), the CV risk was 1.96-fold that of placebo when rofecoxib treatment period exceeded 18 months. On the basis of these results, Merck (USA) discontinued the distribution of rofecoxib and voluntarily recalled the product. One study (the APC Study [61]) revealed that celecoxib elevated the CV risk when used at high doses and for long periods of time. The results of other randomized controlled trials (the PreSAP Trial [62] and the ADAPT [63]) similar to

APC Study, however, showed that the CV risk with celecoxib was comparable to that with placebo or conventional NSAIDs. On the basis of the available evidence, the Advisory Committee of the Food and Drug Administration (FDA) reported that the benefits of celecoxib outweighed its risks. In subsequent epidemiological analysis that investigated whether CV events were related to NSAID usage, conventional NSAIDs were found to elevate CV risk, while the risk due to celecoxib was identified in only 1 out of 17 studies (table 6 [64–76], table 7 [77–91]). Thus, the FDA judged that the CV risk is not related to the class effect of selective COX-2 in-

CV risk								
celecoxib	rofecoxib	meloxicam	diclofenac	ibuprofen	naproxen	other NSAIDs	nonselective NSAIDs	nonusers
0.89 (0.83, 0.94)	1.22 (1.14, 1.30)		0.91 (0.74, 1.13)	0.96 (0.83, 1.10)	0.79 (0.67, 0.93)		0.87 (0.79, 0.96)	1 (ref.)
	3.38 (1.48, 7.74)		1.60 (1.00, 2.57)	1.47 (0.73, 3.00)	2.63 (1.47, 4.72)			1 (ref.)
0.97 (0.86, 1.10)	1.14 (1.00, 1.31)		1.17 (0.96, 1.43)	1.04 (0.68, 1.59)	1.16 (0.89, 1.51)	1 ^a (ref.)		
1.13 (0.70, 1.83)	1.59 (0.87, 2.90)			1 (ref.)	0.86 (0.53, 1.40)	0.82 ^b (0.48, 1.40)		
0.78 (0.63, 0.96)	0.91 (0.76, 1.09)	1 (ref.)						
0.84 (0.63, 1.10)	1.01 (0.82, 1.24)	1 (ref.)						
0.81 (0.70, 0.93)	0.93 (0.83, 1.05)	1 (ref.)						
0.79 (0.60, 1.03)	0.98 (0.80, 1.21)	1 (ref.)						
1 (ref.)	1.27 (1.09, 1.49)					1.26 (1.00, 1.57)		
0.99 (0.87, 1.13)	1.16 (1.01, 1.34)		1.43 (1.01, 2.03)	1.02 (0.75, 1.38)	0.67 (0.45, 0.98)	1.06 ^c (0.75, 1.50)	0.77 ^d (0.60, 0.99)	1 (ref.)
1.00 (0.92, 1.09)	1.15 (1.04, 1.26)		0.98 (0.75, 1.29)	0.95 (0.78, 1.16)	0.83 (0.67, 1.04)	0.93 ^c (0.74, 1.18)	1.02 ^d (0.88, 1.17)	1 (ref.)
1.0 (0.8, 1.3)	1.8 (1.5, 2.2)						1.4 ^e (1.0, 1.9)	1 (ref.)
0.9 (0.7, 1.2)	1.0 (0.8, 1.4)				1.0 (0.6, 1.7)		1.2 ^f (0.9, 1.4)	1 (ref.)
				1.15 (1.02, 1.28)	0.95 (0.82, 1.09)	1.03 (0.92, 1.16)		1 (ref.)
0.88 (0.67, 1.16)	≤25 mg 1.02 (0.76, 1.37) >25 mg 1.93 (1.09, 3.43)			1.01 (0.77, 1.33)	0.92 (0.73, 1.16)			1 (ref.)
2.18 (1.09, 4.35)	2.16 (1.04, 4.46)				1 (ref.)	1.32 ^b (0.81, 2.16)		
0.00 (ref.)	1.40 (−0.20, 3.01)		6.07 (−0.02, 12.15)	−0.01 (−2.49, 2.46)	−0.30 (−2.74, 2.14)			

hibitors. Thereafter, the FDA required that all pharmaceutical companies should add a warning regarding CV and GI bleeding risks on the package insert of all NSAIDs, except aspirin.

Therefore, all NSAIDs should be used with caution or avoided when possible, especially in subjects who have a history of CV events, although the incidence of ischemic heart disease is lower in Japanese and Korean populations than in Western populations according to the Organization for Economic Co-operation and Development (OECD) data [92].

Renal Disorders

Inhibition of PG synthesis in the kidney may result in edema and elevated blood pressure. PGs have been shown to be synthesized in the kidney through a mechanism mediated by both COX-1 and COX-2. Therefore, both NSAIDs and selective COX-2 inhibitors are likely to decrease PG synthesis in the kidney. However, in a combined analysis of the data from 3 studies conducted in Japan [43], the incidence of adverse events associated with edema was significantly lower in the celecoxib treatment group than in the loxoprofen sodium group. Furthermore, the magnitude of change in the systolic and dia-

Table 7. Risk of CV events in case-control studies on NSAIDs

Authors/year of publication	Nested	Number		Outcome evaluation	
		cases	controls		
Varas-Lorenzo et al. [77]/2009	Yes	3,252	20,002	Odds ratio	Acute myocardial infarction
Andersohn et al. [78]/2006	Yes	3,094	11,859	Odds ratio	Ischemic stroke
Kimmel et al. [79]/2005	No	1,718	6,800	Odds ratio	Nonfatal myocardial infarction
Graham et al. [80]/2005	Yes	8,143	31,496	Odds ratio	Acute myocardial infarction
Hippisley-Cox and Coupland [81]/2005	Yes	9,218	86,349	Odds ratio	Myocardial infarction
Fischer et al. [82]/2005	No	8,688	33,923	Odds ratio	Acute myocardial infarction
Solomon et al. [83]/2004	No	10,895	43,580	Odds ratio	Acute myocardial infarction
García Rodríguez et al. [84]/2004	Yes	4,975	20,000	Odds ratio	Acute myocardial infarction, death due to coronary heart disease
Bak et al. [85]/2003	Yes	659	40,000	Odds ratio	Intracerebral hemorrhage
		2,717			Ischemic stroke
Schlienger et al. [86]/2002	No	3,319	13,139	Odds ratio	Acute myocardial infarction
Watson et al. [87]/2002	No	809	2,285	Odds ratio	Myocardial infarction, sudden death, stroke
Huerta et al. [88]/2006	Yes	1,396	5,000	Relative risk	Hospitalization for heart failure
García Rodríguez and González-Pérez [89]/2005	Yes	4,975	20,000	Relative risk	Acute myocardial infarction
Johnsen et al. [90]/2005	No	10,280	102,797	Relative risk	Hospitalization for myocardial infarction
Brophy et al. [91]/2007	Yes	3,423	68,456	Rate ratio	Acute myocardial infarction

A Medline search of articles published between 1999 and 2009 was performed to search for the terms 'nonsteroidal antiinflammatory drugs', 'cardiovascular risk', and 'epidemiology'. The search was restricted to studies on adult humans and case-control studies. Values represent 95% confidence intervals.

^a Meloxicam, etoricoxib, etodolac, and valdecoxib. ^b Other nonselective NSAIDs. ^c Etodolac, tiaprofenic acid, ketoprofen, tenoxicam, nabumetone,

diclofenac combination, tolfenamic acid, meloxicam, sulindac, aceclofenac, flurbiprofen, tolmetin, phenylbutazone, azapropazone, dexibuprofen, fenbufen, and proquazone. ^d Aceclofenac, acemetacin, azapropazone, etodolac, fenbufen, fenoprofen, flurbiprofen, mefenamic acid, nabumetone, tenoxicam, tiaprofenic acid, and sulindac. ^e Other COX-2-selective inhibitor NSAIDs. ^f Nonaspirin NSAIDs.

CV risk										
celecoxib	rofecoxib	meloxicam	diclofenac	ibuprofen	naproxen	indomethacin	piroxicam	other NSAIDs	nonselective NSAIDs	non-users
1.11 (0.84, 1.48)	1.32 (0.91, 1.91)		0.92 (0.57, 1.49)	2.20 (1.06, 4.58)	1.38 (0.73, 2.63)	1.31 (0.67, 2.59)		1.76 (0.56, 5.61)		1 (ref.)
1.07 (0.79, 1.44)	1.71 (1.33, 2.18)		1.32 (1.10, 1.57)	1.12 (0.91, 1.37)	1.16 (0.80, 1.70)			1.20 (1.02, 1.40)		1 (ref.)
0.43 (0.23, 0.79)	1.16 (0.70, 1.93)								0.61 (0.52, 0.71)	1 (ref.)
0.84 (0.67, 1.04)	≤25 mg 1.23 (0.89, 1.71) >25 mg 3.00 (1.09, 8.31)			1.06 (0.96, 1.17)	1.14 (1.00, 1.30)			1.13 (1.01, 1.27)		1 (ref.)
1 (ref.)	≤25 mg 1.47 (0.99, 2.17) >25 mg 3.58 (1.27, 10.11)			1.26 (1.00, 1.60)	1.36 (1.06, 1.75)			1.35 (1.06, 1.72)		
1.21 (0.96, 1.54)	1.32 (1.09, 1.61)		1.55 (1.39, 1.72)	1.24 (1.11, 1.39)	1.27 (1.01, 1.60)			1.27 ^a (1.00, 1.61)	1.21 ^b (1.02, 1.44)	1 (ref.)
			1.23 (1.00, 1.51)	1.16 (0.92, 1.46)	0.96 (0.66, 1.38)	1.36 (0.82, 2.25)	0.95 (0.53, 1.69)			1 (ref.)
1 (ref.)	1.24 (1.05, 1.46)									
0.93 (0.84, 1.02)	1.14 (1.00, 1.31)									1 (ref.)
0.95 (0.74, 1.21)	1.17 (0.90, 1.52)				1 (ref.)					
0.98 (0.76, 1.26)	1.21 (0.92, 1.58)			1 (ref.)						
0.95 (0.82, 1.10)	1.17 (0.99, 1.38)							1 (ref.)		
		0.97 (0.60, 1.56)	1.18 (0.99, 1.40)	1.06 (0.87, 1.29)	0.89 (0.64, 1.24)	0.86 (0.56, 1.32)	1.25 (0.69, 2.25)	0.89 (0.63, 1.25)		1 (ref.)
			1.3 (0.6, 2.8)	1.3 (0.9, 2.0)	0.8 (0.3, 2.1)	1.3 (0.5, 3.7)	0.4 (0.1, 3.1)	1.2 ^c (0.6, 2.1)		1 (ref.)
			1.1 (0.7, 1.7)	1.3 (1.0, 1.6)	0.7 (0.4, 1.1)	1.4 (0.8, 2.4)	0.5 (0.2, 1.3)	1.2 ^c (0.9, 1.6)		1 (ref.)
			1.38 (1.08, 1.77)	1.17 (0.87, 1.58)	0.68 (0.42, 1.13)	1.03 (0.58, 1.85)	1.65 (0.78, 3.49)			1 (ref.)
					0.61 (0.39, 0.94)					1 (ref.)
		0.66 (0.24, 1.83)	1.08 (0.76, 1.52)	1.43 (1.01, 2.02)	2.01 (1.08, 3.74)	3.39 (1.50, 7.67)	1.38 (0.58, 3.28)	1.42 ^d (0.76, 2.68)		1 (ref.)
			1.17 (0.98, 1.40)	1.05 (0.86, 1.28)	0.89 (0.64, 1.25)					1 (ref.)
1.25 (0.97, 1.62)	1.80 (1.47, 2.21)				1.50 (0.99, 2.29)			1.45 ^e (1.09, 1.93)	1.68 ^f (1.52, 1.85)	1 (ref.)
1.08 (0.94, 1.25)	1.28 (1.10, 1.49)	0.78 (0.36, 1.68)			1.24 (0.83, 1.84)				1.00 ^f (0.75, 1.34)	1 (ref.)

stolic blood pressure was also significantly smaller in the celecoxib group than in the loxoprofen sodium group. These data are consistent with the results of the CLASS study [93], where the magnitude of change in serum creatinine level and creatinine clearance from the pretreatment baseline level was shown to be smaller in the celecoxib treatment group than in the diclofenac or ibuprofen treatment groups in patients with RA or OA. Taken together, these results suggest that the impact of celecoxib on the kidneys is relatively small.

Positioning of Celecoxib in Guidelines

Often RA treatment is based on the ACR guidelines published in 2002 [94] and the disease activity score recommended by the European League Against Rheumatism (EULAR). The *Diagnostic Manual and EBM-Based Treatment Guidelines* were published in 2004 by the Japan Rheumatism Foundation (JRF) [95]. A basic approach to RA treatment is to suppress the progression of bone/cartilage destruction and improve long-term prognosis through treatment with antirheumatic drugs, biologic agents, etc., while maintaining the quality of life of patients with the use of NSAIDs and steroids [95]. In both the ACR and JRF guidelines, NSAIDs are deemed as the drugs that are recommended to be used from the early phases of treatment to control inflammation and pain. However, NSAIDs do not appear to have any effect in preventing articular destruction; NSAIDs are administered as the auxiliary treatment to alleviate the symptoms.

The Osteoarthritis Research Society International (OARSI) published its guidelines on the treatment of OA in 2 parts, part I and II, in 2007 and 2008, respectively. In part I [96], the published papers on the effects of selective COX-2 inhibitors, NSAIDs + PPIs, and NSAIDs + misoprostol for OA treatment were grouped as category Ia with the highest evidence level (meta-analysis, randomized comparative study), and their recommendation rate was 100%. In part II [97], it was recommended that NSAIDs should be used at the minimum effective dose for the treatment of OA, while avoiding prolonged use; patients at an elevated risk for GI disorders should be treated with a combination of a selective COX-2 inhibitor or NSAID + PPI or misoprostol, and these drugs were to be used with particular care in patients with CV risk factors.

Conclusion

In this review, we overviewed the data of the Japanese trials that compared the efficacy and safety of celecoxib with those of loxoprofen and compared the celecoxib trial data with those of celecoxib trials published in the West. We also evaluated the safety and usefulness of celecoxib in Japanese subjects with RA, OA, or low back pain. Loxoprofen is a well-known fast-acting analgesic agent and is known to be fairly safe because of its nature of a prodrug, and not similar to those of other NSAIDs that may directly harm the gastric mucosa; therefore, loxoprofen is widely prescribed in Asia. However, in the trials conducted in Japan, with regard to self-assessment of pain by RA patients, celecoxib induced more rapid improvement than loxoprofen, thereby suggesting that celecoxib is more than equivalent to loxoprofen in terms of efficacy. With regard to GI injury that may usually develop in long-term NSAID users, the rates of incidences of symptomatic ulcers and hemorrhagic events in patients treated with celecoxib were significantly lower than the corresponding rates in patients treated with loxoprofen. In addition, the rate of occurrence of CV events in subjects treated with celecoxib was comparable to those in subjects treated with loxoprofen and placebo. All these data are consistent with those reported in the West, thereby suggesting that the use of celecoxib is preferred over conventional NSAIDs like loxoprofen to prevent NSAID-associated GI injury, which still remains highly prevalent and unchanged in Japan.

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