Non-steroidal anti-inflammatory drugs (NSAIDs) like aspirin demonstrate anti-inflammatory effects such as antipyretic or analgesic actions, by inhibiting cyclooxygenase (COX), a rate-limiting enzyme producing prostaglandin (PG), involved in fever and pain. It is known that there are two COX isozymes, designated as COX-1 and COX-2. However, while COX-1 is expressed constitutively in almost all organs, COX-2 is expressed in very limited fashion throughout most tissues unless induced by inflammatory stimuli or mitogens. PGs not only exacerbate inflammation, but also have a significant effect on living organisms to protect gastric mucosa or adjust kidney function. COX-1 is thought to be related to the production of PGs, which have this protective effect on the gastrointestinal tract. However, classical NSAIDs inhibit not only COX-2, which in the inflammatory process acts to produce PGs thus causing fever and pain, but also inhibit COX-1, causing gastrointestinal tract disorders such as gastric ulcers. Hence, both domestic and international pharmaceutical companies launched the development of COX-2 selective inhibitors, hoping that if it is possible to isolate and inhibit COX-2, a new NSAID “Super aspirin” without adverse effects on the digestive system can be created. As a result, celecoxib (trade name: Celebrex), valdecoxib (trade name: Bextra) by Pfizer, rofecoxib (trade name: Vioxx) by Merck, and so forth were developed (Fig. 1).

Although COX-2 selective inhibitors were developed as anti-inflammatory drugs with less adverse effects, it was subsequently found to be effective in preventing the recurrence of cancer. In spite of it being known for some time from epidemiologic data that aspirin is effective in preventing recurrences of colon cancer, it became evident that COX-2 is excessively expressed not only in colon cancer tissues, but also in many other cancer tissues and that COX-2 inhibitors suppressed the occurrence and progression of cancer in animal models. In response to these results, Merck and Pfizer carried out clinical trials to validate the effects of preventing the recurrence of colorectal adenoma in patients with a previous history of the disease. However, in the clinical trial, adenomatous polyp prevention on Vioxx study (APPROVe) by Merck, contrary to their expectations, it was revealed that rofecoxib increased the risk of cardiovascular disease. After a year or more of treatment, differences in the occurrence of myocardial infarction and thrombotic apoplectic stroke gradually appeared between the placebo group and the rofecoxib group. After 18 months of treatment, with daily doses of 25 mg of rofecoxib, the rofecoxib group showed an increase in the risk of critical thromboembolic events, with a relative risk of 1.92, as compared to the placebo group. In response to these results, Merck in the United States immediately suspended the sales of this drug, which was making annual sales of 2,500 million US dollars as of September 2004 and ordered a recall. Furthermore, the clinical trials of rofecoxib in Japan, which were underway at the
time, were discontinued. However, at that time, it was insisted that naproxen had cardioprotective effects.

On the other hand, in a long-term trial studying the effects of celecoxib on cancer patients, Pfizer reported no increase of cardiovascular risk. COX-2 selective inhibitors are classified into sulfones and sulfonamides. Rofecoxib is a sulfone, while celecoxib and valdecoxib are sulfonamides (Fig. 1). Sulfone COX-2 inhibitors promote oxidation of lipoprotein, unlike sulfonamide COX-2 inhibitors. Based on their different constitutions, COX-2 inhibitors are reported to have different effects in increasing the risk of cardiovascular diseases. However, in the APC trial (adenoma prevention with celecoxib) by the National Cancer Institute, the results differed from those of the report by Pfizer. A daily celecoxib dose of 400 mg also increased the risk of cardiovascular diseases 3.4 times. Although there are differences in their effects, almost all of COX-2 inhibitors increase the risk of cardiovascular disease.

Currently, the mechanism with which COX-2 inhibitors increase cardiovascular risk is thought to be attributed to the break-down of the production balance of thromboxane A2 (TXA2) and prostacyclin (PGI2). Although TXA2 and PGI2 are both produced by COX, they demonstrate totally opposite effects (Fig. 2). TXA2, which has vasoconstrictive and platelet-aggregating effects, is produced by COX-1 from platelets. On the other hand, PGI2, which has vasodilatory effects and inhibits platelet aggregation, is produced from vascular endothelial cells. In vascular endothelial cells, PGI2 is also produced by COX-1, but in many cases, COX-2 is synthesized in response to extracellular stimulus, for instance, in accordance to the alteration of blood flow from variation in blood pressure, producing PGI2. In our

In fact, the risk of rofecoxib was expected to some extent in the VIGOR trial (Vioxx Gastrointestinal Outcomes Research), which evaluated its effects on the gastrointestinal tract. This research, which compared rofecoxib with the classical NSAID, naproxen, indicated that the risk of occurrences of gastrointestinal tract disorders was half with rofecoxib, although the occurrence of myocardial infarction was in turn 5 times more. However, at that time, it was insisted that naproxen had cardioprotective effects.
bodies, the production balance of TXA2, which is produced by COX-1 in the platelets, and PGI2, which is produced by COX-2 in vascular endothelial cells, is kept steady and blood flow and clot formation are adjusted. Since classical NSAIDs inhibit both COX-1 and COX-2, it does not upset this balance. However, it is thought that when a drug which inhibits COX-2 only is used, while TXA2 in platelets remains unaffected, PGI2 synthesis in vascular endothelial cells is inhibited, resulting in an increase in platelet aggregation and the risk of cardiovascular diseases such as atherosclerosis or thrombosis. For this reason, although rofecoxib demonstrates higher selectivity than celecoxib, some researchers think that inhibitors with a high specificity against COX-2 may indicate prominent increase in the risk of cardiovascular diseases.

Although the use of rofecoxib has been discontinued, other COX-2 inhibitors are still on the market. Furthermore, some companies are still developing drugs which have COX-2 inhibitory effects. It is true that COX-2 has merits without adverse effects of gastrointestinal tract disorders. For the future, it is deemed important to recognize the increased risk of cardiovascular diseases with COX-2 inhibitors and use these drugs properly by not administering them to patients with cardiovascular diseases like ischemic heart disease.

References