Mini-Review

Update on Cyclooxygenase-2 Inhibitors

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Nonsteroidal anti-inflammatory drugs represent the most commonly used medications for the treatment of pain and inflammation, but numerous well-described side effects can limit their use. Cyclooxygenase-2 (COX-2) inhibitors were initially touted as a therapeutic strategy to avoid not only the gastrointestinal but also the renal and cardiovascular side effects of nonspecific nonsteroidal anti-inflammatory drugs. However, in the kidney, COX-2 is constitutively expressed and is highly regulated in response to alterations in intravascular volume. COX-2 metabolites have been implicated in mediation of renin release, regulation of sodium excretion, and maintenance of renal blood flow. This review summarizes the current state of knowledge about both renal and cardiovascular side effects that are attributed to COX-2 selective inhibitors.

Nonsteroidal anti-inflammatory drugs (NSAID) are the most commonly used class of medications for the treatment of pain and inflammation and represent one of the most common classes of medications used worldwide, with an estimated usage of >30 million per day (1). Nonselective NSAID inhibit both constitutive cyclooxygenase-1 (COX-1) and inducible cyclooxygenase-2 (COX-2), the rate-limiting enzymes that are involved in production of prostaglandins and thromboxane. In addition to their role in inflammation, prostaglandins are important regulators of vascular tone, salt and water balance, and renin release, and nonselective NSAID exhibit adverse effects, including salt retention and reduced GFR, which may elevate BP or make pre-existing hypertension worse (2). It has been estimated that as many as 2.5 million Americans experience NSAID-mediated renal effects yearly (3). Risk factors that predispose to NSAID-induced renal functional alterations include age >65 yr, cardiovascular disease, diabetes, male gender, high NSAID dosage, and concurrent use of other nephrotoxic drugs (3). Up to 20% of patients who take nonselective NSAID and have more than one of these risk factors may manifest alterations in renal function.

In addition to renal side effects, nonselective NSAID have long been known to predispose to gastrointestinal (GI) toxicity. It has been estimated that one third of patients who taking long-term nonselective NSAID develop endoscopically proven gastric or duodenal ulcers (4). The risk for serious bleeding from these lesions is somewhat lower, with approximately 100,000 hospitalizations for GI complications of NSAID (5). One study estimated that nonselective NSAID–induced GI abnormalities constitute the 15th leading cause of death in the United States (6). The premise that COX-1 performs cellular "housekeeping" functions for normal physiologic activity and is the predominant isoform expressed in platelets and the GI tract,

whereas COX-2 acts at inflammatory sites, led to the development of COX-2 selective inhibitors. It also was originally hypothesized that the renal effects of nonselective NSAID were also linked to COX-1 inhibition, but the widespread use of selective COX-2 inhibitors has indicated important roles for COX-2 metabolites in both physiologic and pathophysiologic modulation of renal and cardiovascular function, as highlighted by recent restrictions in the marketing and availability of these agents.

It is important to recognize that there is a wide range in the relative selectivity of various agents to inhibit COX-1 and COX-2. For example, *in vivo*, low-dose aspirin has greater relative COX-1 inhibitory selectivity, acting presystemically at relatively higher concentrations on the COX-1–rich platelet as it passes through the portal circulation, as the aspirin is absorbed (7,8). At high doses, aspirin inhibits both COX isoforms. The relative selectivity of different agents can be measured by *ex vivo* assays of prostaglandin production in whole blood, with the ratio of the concentrations producing 50% inhibition of COX-2 *versus* COX-1 as a measure of selectivity. For such agents, the following COX-2 selectivity ratio can be inferred: Etoricoxib > valdecoxib > rofecoxib > celecoxib > nimesulide > etodolac > meloxicam = diclofenac > indomethacin (9,10).

Expression of COX-1 and COX-2 in the Kidney

COX-1 is expressed constitutively in the kidney and has been localized to mesangial cells, arteriolar smooth muscle and endothelial cells, parietal epithelial cells of Bowman's capsule, and cortical and medullary collecting ducts (11,12). COX-2 is inducible in most tissues in response to injury or inflammation, but COX-2 mRNA and immunoreactive protein are present at detectable levels in normal adult mammalian kidney. In the renal cortex, there is localized expression of COX-2 mRNA and immunoreactive protein in the cells of the macula densa (MD) and in scattered cells in the cortical thick ascending limb cells immediately adjacent to the MD (13–18) (Figure 1A). In human
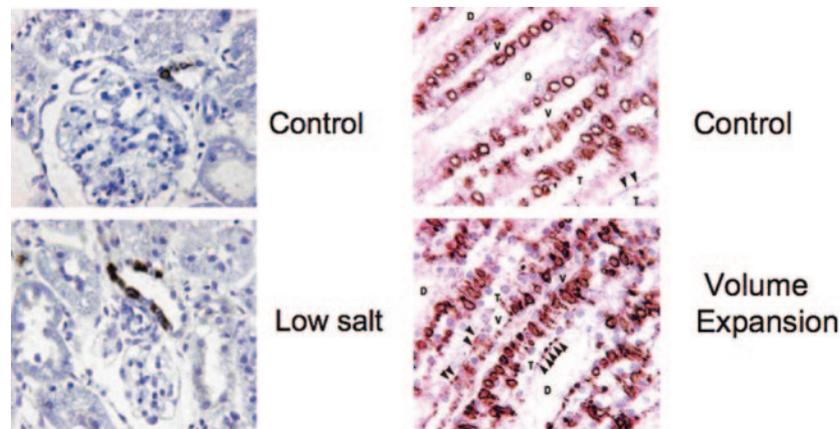
Figure 1. Effect of alterations in dietary sodium on cortical (left) and medullary (right) cyclooxygenase 2 (COX-2) expression. Cortical COX-2 expression is localized to the macula densa and surrounding cTALH cells and increases with a low-salt diet. Medullary COX-2 expression is localized to interstitial cells and increases with a high-salt diet.

kidney, COX-2 expression also has been reported to be present in podocytes and arteriolar smooth muscle cells (12,14,19).

COX-2 expression is also abundant in the lipid-laden medullary interstitial cells in the inner medulla and papilla (13,15) (Figure 1B). Some investigators have reported that COX-2 may also be expressed in inner medullary collecting duct cells or intercalated cells in the renal cortex (20,21). Nevertheless constitutively expressed COX-1 is clearly the most abundant isoform in the collecting duct, so the expression and physiologic significance of COX-2 co-expression in these cells remains uncertain. A recent report in human kidney has suggested that there is also significant COX-2 expression in the medullary vasa recta (19).

Effect of COX-2 Inhibitors on Salt and Water Homeostasis and BP

Nonselective NSAID have been reported to induce peripheral edema in up to 5% of the general population (22). Medullary prostaglandin E_2 (PGE_2) plays an important role in regulating NaCl and water reabsorption in the medullary thick ascending limb and collecting duct (23,24). Because COX-1 is abundantly and constitutively expressed in both cortical and medullary collecting duct, COX-1–derived prostanoids have been hypothesized to be involved in the natriuretic response, and in this regard, acutely increasing renal interstitial hydrostatic pressure by direct renal interstitial volume expansion will induce increased sodium excretion, which is blunted by infusion of nonselective NSAID but not COX-2 inhibitors (25). Furthermore, in a rat model of cirrhosis and ascites, a COX-1 selective inhibitor but not a COX-2 selective inhibitor decreased sodium excretion and impaired the diuretic and natriuretic responses to furosemide (26). Other studies in normal mice also suggest that COX-1 inhibition does not promote natriuresis and may actually promote sodium retention, so the role of renal COX-1 in modulating sodium excretion may be context dependent (27,28).

It is now increasingly apparent that medullary COX-2 plays a critical role in promoting natriuresis when dietary sodium

intake is high. Recent compelling evidence indicates that the renal medulla is a critical site of intrarenal COX-2 activity's protection against the development of systemic hypertension during high-salt intake (29). These studies showed that selective intramedullary infusion of a COX-2 inhibitor or COX-2 antisense oligonucleotides caused animals to develop hypertension when they were placed on a high-salt diet. Because renal medullary COX-2 is expressed primarily in medullary interstitial cells (15,28,30), these studies suggest a critical role for the medullary interstitial cell in maintaining systemic BP.

Renal medullary interstitial cells (RMIC) represent a unique stromal cell that resides between tubule epithelial cells of thick limbs and collecting ducts (31,32) and vasa rectae in the renal medulla. RMIC are morphologically distinguished by the presence of abundant lipid-rich intracellular droplets that are composed of long-chain unsaturated fatty acids, including arachidonate (31,32). RMIC are also distinguished by their robust PGE_2 production rates (30). This locally produced PGE_2 is able to exert its well-described dilator effects on the vasa rectae (33,34) and inhibit salt absorption by the thick ascending limb and collecting ducts *via* basolateral PGE_2 receptors (35,36). Thus, RMIC-derived PGE_2 is positioned at a nexus of physiologic control and can modulate renal salt excretion by affecting both the tone of the vasa recta and epithelial salt absorption. In the context of the current knowledge, RMIC COX-2 seems to be the critical synthetic step for this production of PGE_2 and possibly other natriuretic eicosanoids that are derived from RMIC.

High-salt diet markedly increases renal medullary COX-2 expression both *in vivo* and *in vitro* (37,38). This may be *via* a direct effect of increased interstitial concentration because it has been shown that high extracellular NaCl but not urea potently induces RMIC COX-2 expression (38). When considered together with studies that show that COX-2 inhibition reduces urine salt excretion (39–41) and the findings that the intramedullary COX-2 inhibition produces salt-dependent hypertension (29), a physiologic feedback system can be constructed whereby increased salt intake augments RMIC COX-2 expression and

PG production, thereby promoting increased renal salt excretion, maintaining normal total body sodium content.

COX-2 inhibitors will cause sodium retention occasionally in humans without renal impairment (42–45), and in balance studies that were performed in a clinical research center environment, administration of COX-2 inhibitors consistently decreased urinary sodium excretion for the first 72 h of administration (41,46,47). The relative amount of lower extremity edema has been documented to be greater with 25 mg/d rofecoxib than with 200 mg/d of celecoxib (48). Whether these findings are a result of greater potency of this dose of rofecoxib or of its greater selectivity for COX-2 *versus* COX-1 or other factors remains undetermined.

Nonselective NSAID may elevate BP and antagonize the BP-lowering effect of antihypertensive medications, including diuretics, angiotensin-converting enzyme (ACE) inhibitors, and β blockers, to an extent that may potentially increase hypertension-related morbidity (49,50). COX-2 inhibitors also have been shown to affect BP. In studies that involved experimental animals, rofecoxib was shown to elevate significantly systolic BP in SHR or WKY rats that were fed a normal-salt or high-salt diet but not a low-salt diet, which suggests that the hypertension that is induced by COX-2 inhibition can occur independent of a genetic predisposition to hypertension and can be prevented by salt deprivation (51). In mice, COX-2 inhibition enhances the pressor effect of angiotensin II (Ang II) (28).

In double-blind, randomized, controlled clinical trials, conflicting results have been obtained about the influence of COX-2 inhibitor treatment on BP. It is somewhat difficult to compare these trials, because there are variations in design, subject characteristics, end points, and methods of BP measurement. In this regard, the two large trials that investigated the safety of COX-2 inhibitors, the Celecoxib Long-term Arthritis Safety Study (CLASS; Celecoxib) and Vioxx Gastrointestinal Outcome Study (VIGOR; Rofecoxib), both found in a minority of subjects evidence for increased BP less than or equal to (CLASS) or greater than (VIGOR) the NSAID comparators (44,52,53). In a review of clinical studies that involved >13,000 subjects, Whelton *et al.* (54) found that the overall incidence of renal adverse events that were induced by celecoxib was greater than that seen with placebo and was similar to the effects of the NSAID comparators. Because of the high prevalence of NSAID use among people 65 yr old or older, subsequent studies (SUCCESS VI [55] and VII [56]) compared the renal safety in older hypertensive patients with osteoarthritis (890 and 1092 patients in VI and VII, respectively) and found that at week 6, rofecoxib was more likely to increase the systolic BP than celecoxib. Similarly, in patients with type II diabetes and hypertension, ambulatory BP monitoring indicated that unlike celecoxib and the nonselective NSAID comparator naproxen, rofecoxib led to significant increases in 24-h systolic BP, although all three drugs induced some destabilization of BP control (57). Rofecoxib caused the greatest increase in systolic BP in patients who received ACE inhibitors or β blockers, whereas those who were on calcium channel antagonists or diuretic monotherapy and received either celecoxib or rofecoxib showed no significant increases in BP. However, in a randomized, double-blind, placebo-controlled, parallel-group clinical trial that involved 178 patients with essential hypertension and that used 24-h ambulatory recordings and high doses (400 mg/d, twice the recommended dose) of celecoxib, there was no evidence of any significant alteration of the antihypertensive effect of the ACE inhibitor lisinopril during a 4-wk period (58). Interpretation of these studies is complicated by uncertainty about comparisons of equivalence of potency and duration of action of the two coxibs (rofecoxib and celecoxib).

Effects of COX-2 Inhibitors on Renin and Renal Hemodynamics

In the mammalian kidney, the MD is involved in regulating afferent arteriolar tone and renin release by sensing alterations in luminal chloride *via* changes in the rate of $Na^+/K^+/2Cl^-$ co-transport (59,60). COX-2 expression increases in the MD in response to a salt-deficient diet and decreases in response to a high-salt diet (13,37). MD sensing of luminal chloride concentration is dependent on net apical transport, mediated by the luminal $Na^+/K^+/2Cl^-$ co-transport (61). Ion substitution experiments of tubular perfusate have shown that low extracellular chloride leads to increased renin secretion (62). Decreased extracellular chloride also has been demonstrated to upregulate COX-2 expression in MD/cortical thick ascending limb, primarily through a mitogen-activated protein kinase–dependent pathway (63,64) *via* NF-κB activation (65). In addition, reducing luminal $[Cl^-]$ in microperfused cortical thick limb has been found to be associated with increased COX-2–dependent basolateral PGE_2 release from the MD, further suggesting that COX-2–derived metabolites exert paracrine effects on renin release and arteriolar tone in the neighboring juxtaglomerular apparatus (66).

Measurements *in vivo* in isolated perfused rat kidney and in isolated perfused juxtaglomerular (JG) preparations all indicated that administration of nonspecific COX inhibitors prevents the increases in renin release that are mediated by MD sensing of decreases in luminal NaCl (reviewed in [67,68]). Studies using experimental animals have indicated that selective COX-2 inhibitors can significantly decrease plasma renin levels, renal renin activity, and mRNA expression under certain high-renin states (69–75). Most (43,64,66,69,70,76–78) but not all experimental studies (79,80) have indicated a role for COX-2 in MD mediation of renin release. Randomized crossover studies in healthy humans who were administered furosemide and/or a low-sodium diet demonstrated inhibition of renin release by the COX-2 inhibitors rofecoxib (43) and meloxicam (81). In addition, in patients with hyperprostaglandin E syndrome/antenatal Bartter's syndrome, who have genetic abnormalities in thick limb/MD NaCl reabsorption, rofecoxib administration suppresses hyperreninemia as effectively as indomethacin, further supporting a role for COX-2 metabolites in mediation of renin release (82,83).

Studies of prostanoid-dependent control of renal blood flow (RBF) and GFR by the MD indicate that both vasodilator and vasoconstrictor prostanoids may contribute to regulation of tubuloglomerular feedback (60,84–86). In addition, COX-2–derived prostanoids from vascular endothelium may directly

modulate afferent arteriolar tone. Vasodilatory PG seem to be critical for maintaining RBF and GFR during volume-depleted states associated with increased circulating vasoconstrictors, such as Ang II or norepinephrine, by blunting constriction of the afferent arteriole (87). By inhibiting the production of PG that contribute to maintenance of vasodilation of adjacent afferent arterioles, COX-2 inhibition may contribute to the decline in GFR that is observed in patients who take NSAID or selective COX-2 inhibitors (88). In anesthetized dogs, nimesulide administration increased arterial pressure and decreased RBF, urine flow rate, and fractional lithium excretion in those that were on a low-sodium diet (89,90). Similar findings were reported in isolated perfused rat kidney (73). When renal cortical blood flow (CBF) and medullary blood flow (MBF) were selectively measured in mice, it was found that acute infusion of a COX-1 selective inhibitor did not affect either CBF or MBF. In contrast, a COX-2 selective inhibitor significantly reduced MBF without altering CBF; chronic pretreatment with a COX-1 inhibitor did not modify the effect of Ang II infusion, whereas Ang II significantly reduced MBF in mice that were pretreated with a COX-2 inhibitor or in COX-2 knockout mice (28). In healthy humans who were on normal-sodium diets, COX-2 inhibitors had minimal effects on renal hemodynamics (41,42). However, COX-2 inhibitors significantly decreased GFR in salt-depleted subjects (39,40,46,91). As further evidence of an important role for COX-2 in regulation of renal hemodynamics and renin production, acute ischemic renal insufficiency and hyperkalemia/type IV renal tubular acidosis have been reported as acute nephrotoxic effects of COX-2 inhibitors, especially in the older adults (88,92–95).

Other Renal Complications of COX-2 Inhibitors

Recently, tubulointerstitial injury also was reported with COX-2 inhibitors. One case of celecoxib-related renal papillary necrosis was reported (96), as well as cases of tubulointerstitial nephritis (97,98). A potential interaction between lithium and celecoxib also has been described (99,100).

Effects of COX-2 Inhibitors in Proteinuric States

NSAID have been reported to be effective in reducing proteinuria in patients with refractory nephrotic syndrome (101–104). Selective increases in renal cortical COX-2 expression can be detected in the region of the MD in rat remnant kidneys without significant alterations in COX-1 expression (105–107) and from kidneys with streptozotocin-induced diabetes (108,109). Isolated glomeruli from remnant kidneys also demonstrated selective increases in COX-2 immunoreactivity and increased PGE_2 production, which was inhibited by a COX-2 selective inhibitor (105). Komers *et al.* (108) found that in rats with moderately controlled streptozotocin-induced diabetes, GFR was increased, and acute administration of a selective COX-2 inhibitor returned the GFR to control levels. In hyperfiltering states, tubuloglomerular feedback is reset at a higher distal tubular flow rate (110–112), and there is decreased myo-

genic tone of the afferent arteriole, which is corrected by inhibition of COX activity (113,114). Although we have not yet determined the signals that mediate increased COX-2 expression in this diabetic model, it is worth noting that recent studies indicated that glomerular hyperfiltration in diabetic rats occurs as compensation for increased proximal fractional reabsorption and a decrease in electrolyte load to the distal nephron, resulting in resetting of tubuloglomerular feedback to a higher single nephron GFR (115,116); this increased proximal reabsorption and resultant decrease in distal nephron electrolyte presentation would also be expected to increase MD COX-2 expression. The vasodilatory component of tubuloglomerular feedback is inhibited by the selective COX-2 inhibition, suggesting that COX-2–mediated prostanoids may be essential for arteriolar vasodilation (117,118).

Chronic administration of a selective COX-2 inhibitor significantly decreased proteinuria and inhibited development of glomerular sclerosis in rats with reduced functioning renal mass (105,106,119). These effects were seen in the absence of any detectable changes in systemic BP, suggesting that any "renoprotective" effects that were seen with the COX-2 inhibitor were not secondary to modulation of systemic BP (105,120). In a model of diabetes with superimposed DOCA/salt hypertension, chronic administration of a selective COX-2 inhibitor also significantly decreased proteinuria and reduced extracellular matrix deposition, as indicated by decreases in immunoreactive fibronectin expression and mesangial matrix expansion. In addition, COX-2 inhibition reduced expression of TGF-β, plasminogen activator inhibitor 1, and vascular endothelial growth factor in the kidneys of the diabetic hypertensive animals (109). Obviously, more studies are needed before any recommendation that these drugs be used clinically for these indications.

To summarize the renal side effects of COX-2 inhibitors, it now is evident that similar to nonselective NSAID, selective COX-2 inhibition may cause edema, hypertension, and even acute renal failure in a minority of patients. COX-2 inhibitors also may exacerbate preexisting hypertension or interfere with other antihypertensive drugs. Special caution should be taken in patients with volume depletion or decreased organ perfusion. Although all COX-2 inhibitors that have been marketed have demonstrated the same spectrum of renal side effects, the number and the severity of the side effects has tended to be greater with rofecoxib than with celecoxib. The effective half-life of the former drug is longer, which may be responsible for the increased side effects when both drugs are administered once per day. However, it also is possible that non-"class" effects of the drugs may be a factor because the chemical structures are different, with celecoxib being a sulfonamide and rofecoxib a sulfone (121). Further modifications of these drugs in the future may provide agents with fewer renal side effects.

Recently, nitric oxide donors were shown to prevent renal depletion of prostacyclin during either nonselective or selective COX-inhibitor administration (122). Their combination with NSAID may reduce adverse renal effects. Several distinct agents with balanced inhibitory actions on the COX and lipoxygenase pathways also have been synthesized and are in various

phases of preclinical or clinical development (123,124), and recently, a clinical trial indicated that the lipoxygenase/COX inhibitor licofelone could provide as effective pain relief as celecoxib but with less edema (125).

Cardiovascular Effects of COX-2 Inhibitors
Effects of COX-2 Inhibition on Vascular Tone

In addition to their propensity to reduce renal salt excretion and decrease MBF, NSAID and selective COX-2 inhibitors have been shown to exert direct effects on systemic resistance vessels. The acute pressor effect of Ang infusion in humans was significantly increased at all Ang II doses studied by indomethacin pretreatment (126), an NSAID that nonselectively inhibits both COX-1 and COX-2 (127). More recently, administration of selective COX-2 inhibitors or COX-2 gene knockout has been shown to accentuate the pressor effects of Ang II in mice (28). These studies also showed that the ability of Ang II infusion to produce an increase in BP was markedly reduced by administration of a selective COX-1 inhibitor or COX-1 gene knockout (28). These findings support the conclusion that COX-1–derived PG participate in and are integral to the pressor activity of Ang II, whereas COX-2–derived PG are vasodilators that oppose and mitigate the pressor activity of Ang II. Other animal studies showed that both NSAID and COX-2 inhibitors blunt arteriolar dilation and decrease flow through resistance vessels (128–130).

Increased Cardiovascular Thrombotic Events

COX-2 is known to be induced in vascular endothelial cells in response to shear stress (131), and selective COX-2 inhibition reduces circulating prostacyclin levels in normal humans (132). Therefore, since the development of COX-2 selective antagonists, it has been suggested that these agents might carry increased thrombogenic risks as a result of selective inhibition of the endothelial-derived anti-thrombogenic prostacyclin without any inhibition of the prothrombotic platelet-derived thromboxane generated by COX-1 (133). Although animal studies have provided conflicting results about the role of COX-2 inhibition on development of atherosclerosis (134–138), there are recent indications that COX-2 inhibition may destabilize atherosclerotic plaques (139), as suggested by studies indicating increased COX-2 expression and co-localization with microsomal PGE synthase-1 and metalloproteinases-2 and -9 in carotid plaques from individuals with symptomatic disease before endarterectomy (140–142).

Recently, the cardiovascular risks of COX-2 inhibition were front-page news in both medical and lay media, which has led to considerable confusion and angst among patients and practitioners alike. The first intimation that COX-2 inhibitors could predispose to increased cardiovascular risk arose from VIGOR, which compared GI toxicity in patients who had osteoarthritis or rheumatoid arthritis and received either rofecoxib (50 mg/d) or the nonselective NSAID comparator naproxen (1000 mg/d). The rofecoxib-treated patients were found to have a 2.38 relative risk for serious thrombotic cardiovascular effects (143). Although low-dose aspirin was omitted from this study, the increased risk with rofecoxib was observed regardless of

whether the patients had preexisting cardiovascular risks that would have qualified for aspirin. Although these findings elicited considerable attention (144), the interpretation of the results was controversial for a number of reasons, including that a similar study in osteoarthritis patients that compared celecoxib with other nonspecific comparator NSAID (CLASS) did not detect an increased cardiovascular risk of the COX-2 selective agent (111) and the suggestion that the apparent increased cardiovascular risk seen in VIGOR with rofecoxib was actually due to a preferential beneficial effect of naproxen to inhibit platelet aggregation as a result of naproxen's long half-life (145).

More definitive conclusions about increased cardiovascular risk with rofecoxib were subsequently reported from the Adenomatous Polyp Prevention by Vioxx trial (APPROVe), which compared rofecoxib (25 mg/d) with placebo in patients who had a history of colorectal adenomas. In this study, the rofecoxib group manifested an excess risk for thrombotic cardiovascular events after 18 mo of daily rofecoxib treatment (relative risk 1.92; 95% confidence interval 1.19 to 3.11; $P < 0.008$; Figure 2) (146). In anticipation of the release of these results, Merck voluntarily withdrew rofecoxib from the market in September 2004. The pathophysiologic mechanisms underlying increased cardiovascular risk associated with long-term rofecoxib use remain undetermined but could include increased atherosclerosis, associated hypertension, or other, as yet undetermined concomitant cardiovascular changes.
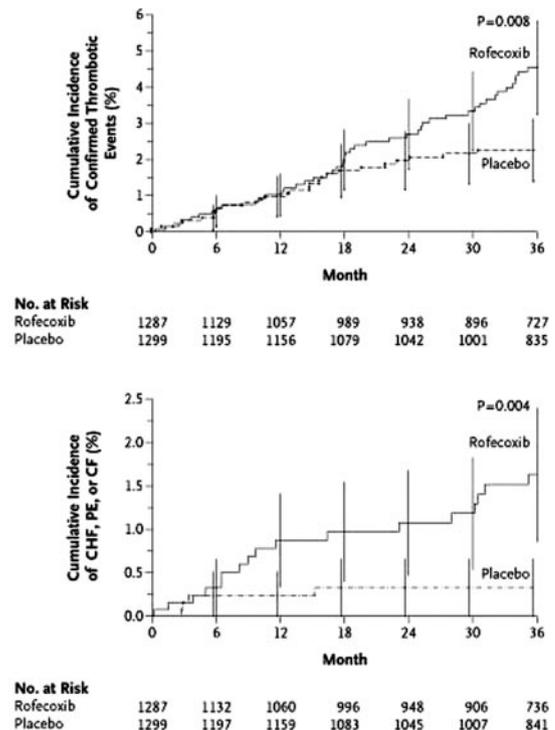

Figure 2. Increased cardiovascular risk with Rofexicab treatment in the APPROVe trial. (Top) Kaplan-Meier estimates of the cumulative incidence of confirmed serious thrombotic events. (Bottom) Estimates of congestive heart failure, pulmonary edema, or cardiac failure. Reprinted with permission from reference (146).

Subsequent to the release of the results from APPROVe, two NIH-sponsored trials that examined celecoxib were halted in late 2004 because of concerns about cardiovascular risk. In the Adenoma Prevention with Celecoxib study, a similar trial to APPROVe that studied prevention of colorectal adenoma formation, an independent Data Safety Monitoring Board concluded that continued exposure to the COX-2 inhibitor would place the patients at increased risk for cardiovascular events (147). In contrast, a study of possible beneficial effects of long-term administration of either naproxen or celecoxib in Alzheimer's disease (Alzheimer's Disease Anti-Inflammatory Prevention Trial) reported a possible increased risk in both cardiovascular and cerebrovascular events in the naproxen-treated group, although this naproxen-induced increase has been questioned (148). Two other epidemiologic studies also highlighted a potential cardiovascular risk of nonselective NSAID as well as COX-2 selective drugs. A study from Denmark reported that there was increased incidence of first-time hospitalization for myocardial infarction in patients who were taking all classes of nonaspirin NSAID (149), and an analysis of 468 practice groups in England reported an increased risk for myocardial infarction in patients who were taking either COX-2 selective or nonselective NSAID (150).

The Food and Drug Administration (FDA) convened a special advisory committee meeting in February 2005 to address these issues. After a contentious three-day meeting, the advisory committee voted (by a vote of 31 to 1) to recommend that celecoxib be retained on the market, by a vote of 17 to 13 that valdecoxib be retained, and by a vote of 17 to 15 that rofecoxib be retained. To date, however, rofecoxib remains off the market, and on April 7, 2005, the FDA ruled that the overall risk-to-benefit profile for valdecoxib was unfavorable and furthermore that valdecoxib did not have any marked advantage over other NSAID. The FDA therefore requested that Pfizer, valdecoxib's manufacturer, voluntarily withdraw it from the market. In the same ruling, the FDA requested that the labeling of celecoxib, as well as 18 other nonselective NSAID, be modified to highlight the increased risk for cardiovascular events, with a medication guide informing patients to accompany all prescriptions.

Acknowledgments

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