

Review

Mechanisms Involved in the Adverse Cardiovascular Effects of Selective Cyclooxygenase-2 Inhibitors

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Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for managing inflammation, but they are associated with gastrointestinal and renal toxicity upon long-term use. Selective cyclooxygenase-2 (COX-2) inhibitors, or coxibs, were developed to avoid these adverse effects while maintaining anti-inflammatory efficacy. However, accumulating evidence indicates that coxibs may increase the risk of cardiovascular complications. This review explores the pathophysiological mechanisms underlying adverse cardiovascular effects in patients treated with COX-2 inhibitors. These mechanisms include an imbalance between prothrombotic and antithrombotic factors, an altered endocannabinoid metabolism, and downregulation of PPAR δ , contributing to thrombosis. Additionally, COX-2 inhibition disrupts renal prostaglandin synthesis, particularly PGE₂ and prostacyclins, reduces EP₄ receptor expression in macrophages, promotes chemotaxis, and elevates arterial pressure via increased iNOS, ADMA, and L-NMMA activity. At the molecular level, genetic polymorphisms, matrix metalloproteinases, signaling cross-talk, and direct cardiomyocyte injury are implicated. Collectively, these alterations promote a prothrombotic state, fluid retention, enhanced vasoconstriction, impaired vasodilation, myocardial injury, cell death, and cardiac fibrosis. Despite these risks, coxibs are often prescribed without adequate cardiovascular assessment, particularly in patients with pre-existing cardiovascular risk factors. Greater awareness of these mechanisms is essential to optimize the benefit–risk ratio in clinical decision-making involving selective COX-2 inhibitors.

Keywords: coxibs; COX-2 inhibitors; cardiovascular risk; cardiovascular disease; adverse effect



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1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used widely and globally to treat conditions such as rheumatoid arthritis, osteoarthritis [1,2], headache, pain, and dysmenorrhea [3]. However, their long-term use is associated with gastrointestinal and renal damage [4]. That is why, when cyclooxygenase-2 (COX-2) was discovered in 1990, the development of a new group of drugs with the same anti-inflammatory capacity but with fewer adverse effects was promoted [5]. In 1999, the first selective COX-2 inhibitors (coxibs)—celecoxib and rofecoxib—came to light [6]. Little by little, others were added to the list, such as lumiracoxib, parecoxib, valdecoxib, and etoricoxib [7].

Multiple studies conducted on coxibs reveal the risk of adverse cardiovascular events, including acute myocardial infarction (AMI), cerebrovascular events (CVEs), heart failure (HF), systemic arterial hypertension (SAH), and sudden death. This study focuses on showing the possible mechanisms by which coxibs increase cardiovascular risk (CVR), as well as their relevance in medical practice. Among the various theories for the pathogenesis of cardiovascular adverse events, the one most accepted is that, by inhibiting COX-2, the level of prostacyclin—a powerful vasodilator—is reduced. This causes thromboxane-A₂ production to predominate, favoring an prothrombotic environment [4]. However, knowledge of the pathophysiological process by which the increase in CVR occurs remains unclear. It is essential to study and understand the mechanisms involved, because this could help develop a drug with fewer adverse cardiovascular effects without loss of therapeutic efficacy. However, a review of the current literature reveals only a few recent studies about these mechanisms. These works are discussed in the present work below.

2. Definition and Mechanism of Action

Coxibs are non-competitive selective inhibitors of the enzyme COX-2. This enzyme catalyzes the conversion of arachidonic acid to the prostaglandins G₂ and H₂, substances that mediate pain and inflammation. COX-2 is expressed from inflammatory stimuli such as cytokines and growth factors [8,9]. Selective COX-2 inhibitors are classified into three generations (Table 1).

Table 1. Classification of selective COX-2 inhibitors.

Group	Selective COX-2 Inhibitors
First generation	Celecoxib and rofecoxib
Second generation	Valdecoxib and parecoxib
Third generation	Etoricoxib and lumiracoxib

3. Cardiovascular Safety of Coxibs

Since their launch, coxibs have been shown in various clinical trials to have a different safety profile than conventional NSAIDs. This became evident when the VIGOR (Vioxx and Gastrointestinal Outcomes Research) study of 8076 patients was conducted, during which the use of rofecoxib was compared to that of naproxen in people with rheumatoid arthritis, to assess the gastrointestinal safety of the drug. Alarming, however, it was observed that use of rofecoxib, compared to naproxen, involved a higher relative risk (RR: 2.39) of a cardiovascular event [10]. This study generated controversy, which is why multiple other studies were carried out, including the one by Konstam et al. [11], a meta-analysis where no significant difference in CVR was found between rofecoxib and placebo or other NSAIDs, and that of Solomon et al. [12], a matched case-control study of 54,475 patients where the use of rofecoxib was associated with increased CVR. Finally, in 2004, rofecoxib was removed from the market due to the results of the APPROVe (Adenomatous Polyp Prevention on Vioxx) study, in which 2586 patients with colorectal adenomas were treated with rofecoxib

or placebo and it was shown that the rofecoxib group experienced considerably increased CVR and cardiac death [13].

Contrarily, in the case of celecoxib, the CLASS study (Celecoxib Long-term Arthritis Safety Study) was carried out in 2000. This was designed to analyze the gastrointestinal safety of celecoxib, compared to non-selective NSAIDs, in 8059 patients. It was observed that celecoxib had a better gastrointestinal safety profile; however, in terms of CVR there were no significant differences between celecoxib, diclofenac, and ibuprofen. In the VIGOR study, involving only patients with rheumatoid arthritis, use of rofecoxib was associated with high CVR. This can be attributed to the fact that the risk was due to the underlying pathology and not to the medication, because in the CLASS study patients with rheumatoid arthritis had a higher CVR than those with osteoarthritis [14].

Later, in 2005, the APC (Adenoma Prevention with Celecoxib) study of 2035 patients was published. This compared the use of 200 or 400 mg of celecoxib vs. placebo. After 2.8 to 3.1 years of follow-up, the patients who received 200 mg showed an RR of 2.3 for cardiovascular death; among those who took 400 mg, the RR was 3.4 [15]. In the 2016 PRECISION study (Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen), where 24,081 patients were studied, there was no significant difference in CVR between celecoxib and conventional NSAIDs [16]. In the 2017 PRECISION-ABPM substudy, which compared ambulatory blood pressure changes in 444 patients randomized to celecoxib, ibuprofen, or naproxen, celecoxib showed the smallest 24-hour systolic blood pressure increase and the lowest incidence of new-onset hypertension. Ibuprofen produced the largest increase in systolic blood pressure, whereas naproxen showed an intermediate effect [17].

4. Risk of Adverse Cardiovascular Effect in Patients Without Underlying Cardiovascular Disease

The magnitude of the increase in both relative and absolute risk is evidenced in a meta-analysis published by the Coxib and traditional NSAID Trialists' Collaboration (CNT) [18], where data from predominantly individual participants were obtained from randomized trials comparing a coxib with placebo. The clinical trial used data from 289,969 people. Of the total number of participants, only 9% had a history of CVD (cardiovascular disease). At one-year follow-up, major CVDs were found to be increased when compared to placebo for high-dose diclofenac (RR 1.41) and for coxibs (RR 1.37). There was a trend for increased cardiovascular death as an individual coxib endpoint compared to placebo. The use of coxibs in patients with low cardiovascular risk was associated with two adverse events per 1000 people per year.

5. Mechanisms Involved

The mechanism by which coxibs increase the risk of cardiovascular events (HF, SAH, atrial fibrillation, and venous thromboembolism) is controversial, and multiple theories have been postulated, which vary in origin. It is important to note that the different mechanisms are not mutually exclusive but may instead synergize their deleterious effects on cardiovascular health. The different prothrombotic, genetic, molecular, and renal mechanisms described to date are presented below.

5.1. Prothrombotic Mechanisms

5.1.1. Thromboxane A2 and Prostacyclin

In murine models, inhibition of COX-2 is associated with reduction in prostacyclin by vascular endothelium, with little to no inhibition of potentially prothrombotic platelet thromboxane A2 production. This ultimately results in decreased vasodilation and in-

creased vascular smooth muscle contraction and platelet adhesion. The relatively selective reduction in prostacyclin activity could predispose to endothelial damage [19,20].

5.1.2. Thrombomodulin and Protein C

Using microarray chip technology with cultured human smooth muscle cells, it was demonstrated that inhibition of prostacyclin by coxibs also decreases levels of thrombomodulin, which under physiological conditions is responsible for binding to thrombin to activate protein C, which plays an important role in the inhibition of FVa and FVIIIa from the coagulation cascade. These effects also condition the prothrombotic state [21].

5.1.3. Endocannabinoids

Metabolism of endocannabinoids by COX-2 endothelial cells [22] together with prostacyclin synthase activates nuclear peroxisomal proliferator activated receptor δ (PPAR δ), which reduces tissue factor expression (TF), the initiator of the coagulation cascade. In experimental settings, it has been shown that use of coxibs inhibits PPAR δ , which conditions an increase in TF, causing a prothrombotic state. Furthermore, PPAR δ agonists could be used to suppress cardiovascular adverse effects induced by coxibs [23].

5.2. Renal Mechanisms

5.2.1. Prostaglandins and Prostacyclins as Antinatriuretics

Clinical studies have demonstrated that the decrease in the synthesis of PGE2 and prostacyclins is associated with both antinatriuretic and vasoconstrictor effects [24], and that this translates into an acute relative reduction in daily urinary sodium excretion of 30% [25]. In patients with normal renal function, the kidneys will within days increase sodium excretion to offset the anti-natriuretic effects of coxib, in order to maintain sodium homeostasis. However, in patients with chronic kidney disease, this homeostatic process is often impaired, so that within 1 to 2 weeks of starting coxibs a considerable amount of sodium and water may accumulate. In such cases, edema and hypertension commonly develop, as well as congestive heart failure in more severe cases [12].

5.2.2. Proinflammatory Cell Chemotaxis

COX-2 inhibition exacerbates SAH and increases CVR due to decreased COX-2 activity in the renal interstitium, leading to reduced total sodium excreted [26]. One possible mechanism, proposed by Zhang et al. in their experimental study on rats [27], is that macrophages are responsible for releasing cytokines that promote the activation and chemotaxis of proinflammatory immune cells, but they also have a receptor called EP4 on their surface which is activated by prostaglandins to feed back this process of chemotaxis. When prostaglandins are absent, the infiltration of proinflammatory cells in the kidney is promoted, leading to an increase in blood pressure.

5.2.3. Nitric Oxide Synthetase Inhibition

In a transcriptomic study conducted by Ahmetaj-Shala et al. [28], it was found that in COX-2-deficient murine models, there was renal upregulation in the metabolism of iNOS inhibitors, asymmetric dimethylarginine (ADMA) and monomethyl-L-arginine (L-NMMA). The increase in systemic iNOS inhibitors increases peripheral vascular resistance, which translates into higher blood pressure and vascular damage.

5.2.4. Angiotensin-2

Qi et al. [29] showed in mice that COX-2 inhibitors reduce renal medullary blood flow and urinary flow, increasing the vasopressor effect of angiotensin-2, which increases

edema and blood pressure, while inhibition of COX-1 attenuates the vasopressor effect of angiotensin-2.

5.2.5. Aldosterone

Recently, an experiment conducted by Winner et al. showed that coxibs inhibit aldosterone glucuronidation by human renal microsomes, increasing plasma and tissue concentrations of aldosterone, which increases systemic blood pressure by retaining sodium and water [30].

6. Genetic and Molecular Mechanisms

6.1. Single Nucleotide Polymorphisms

In observational studies of humans, 47 genes have been identified whose single nucleotide polymorphisms (SNPs) are associated with coronary disease. Of these genes, those that increase the risk of coronary heart disease to the greatest extent are vascular endothelial growth factor “A” (VEGFA), matrix metalloproteinase (MMP)-9, estrogen resistance protein 1 of cancer of breast (BRCA1), the R-type voltage-dependent gene, and calcium channel alpha subunit E1 (CACNA1E) [31]. The VEGFA gene SNP reduces the expression of this factor, which is critical for vascular permeability, nitric oxide production, and angiogenesis [32]. MMP-9 helps to positively regulate VEGFA, so a decrease in its expression is associated with coronary heart disease [31]. BRCA1 is associated with various forms of cancer, and has also been linked to increased CVR [33]. It is also associated with focal adhesions, as well as regulation of smooth muscle cell migration from the intima media and carotid muscle in vitro, promoting elevation of blood pressure. CACNA1E regulates voltage-dependent calcium channels, which allow calcium access to excitable cells for different neurotransmission processes such as myocardial and vascular contractile processes [34]. The involvement of CACNA1E by coxibs suggests that it raises systemic blood pressure. From what was explained above, we can infer that the interaction of any of these four genes with coxibs can generate a decrease in nitric oxide, angiogenesis, greater migration of smooth muscle cells to the intima of the carotid artery, and alteration of calcium channels. All of these increase the risk of coronary disease. In humans, other associated SNPs include PTGS1, MMP-1, AGT, CRP, Chr9p21.3, and KL [35].

Contrarily, the SNP Prostaglandin-endoperoxide Synthase-1 (PTGS1) is associated with AMI and unstable angina because it reduces the arachidonic acid cascade, resulting in a low concentration of PG-F2 α in vitro. The 3' untranslated region SNP in the C-reactive protein is associated with atherosclerosis, metabolic syndrome, and coronary heart disease [36].

6.2. Metalloproteinases

Likewise, the MMPs can be anti-inflammatory or pro-inflammatory depending on the stimulus [36,37]. A clinical trial demonstrated that COX-2 inhibition reduces the synthesis of PG-E2, PG-EP2, and PG-EP4 (required for modulation of MMPs), thus interfering with the resolution of inflammation. In a setting of COX-2 inhibition by drugs such as rofecoxib and celecoxib, concentrations of MMP-1, MMP-3, and interleukin (IL)-8 increased [38]. MMP-1 and MMP-3 are found in abundance in atherosclerotic plaques and blood vessels. These are associated with plaque rupture, vascular damage, and tissue destruction [39]. For its part, IL-8 overlaps the MMP increase, which has been studied in human cells [40]. In addition, coxibs stimulate the synthesis of tissue plasminogen activator (tPA), which converts plasminogen to plasmin, stimulating production of MMP. Additionally, coxibs reduce the expression of TIMP, the main inhibitor of MMPs, further accentuating vascular damage and increasing the risk of coronary heart disease [38]. Patients expressing the

CYP2C9 genotype (CYP2C9*1/*3 or CYP2C9*3/*3) have lower coxib clearance, which is associated with increased cardiovascular risk [41].

6.3. Crosstalk

In 2013, to observe coxib-associated biochemical and molecular changes in cardiomyocytes, Sakane et al. [42] analyzed a rat cardiac myoblast embryonic cell line called H9c2, which is similar to human cardiac myocytes under the effects of celecoxib. The results suggested that celecoxib causes stress to H9c2 because it induces different signaling pathways (crosstalk) than normal, causing DNA disassembly and a subsequent alteration of its normal function, triggering programmed cell death processes, necrosis, and heart failure. It is speculated that this mechanism, in vivo, is responsible for the increased risk of AMI and CVD in those who regularly use celecoxib.

In the experimental study by Mosaad et al. [43], it was shown that in 70 murine models susceptible to hypertension, celecoxib increased mortality, systolic blood pressure, and cardiac enzymes. Additionally, celecoxib was associated with a proapoptotic effect by the activation of the enzyme caspase-3, increasing the expression of activated caspase-3 and Bax by immunohistochemistry, and decreasing the expression of Mcl-1 and BCL2.

In murine models, coxibs increase the incidence of hypertension and CVR. This is due to the inhibition of COX-2 that diverts the arachidonic acid cascade towards the CYPA1 enzyme, increasing the synthesis of 20-hydroxyeicosatetraenoic acid (vasoconstrictor) and the markers of cardiovascular damage endothelin-1 and brain natriuretic peptide; this effect is greater under the concomitant use of antidiabetics such as rosiglitazone [44]. Table 2 summarizes all mechanisms mentioned above.

Given the evidence, it is crucial to highlight that cardiovascular risk associated with COX-2 inhibitors is dose-dependent and related to duration of use: higher doses and prolonged exposure significantly raise the probability of major adverse cardiovascular events [15,45–47]. It is therefore recommended that the lowest effective dose be used for the shortest possible duration, and that when treatment is needed repeatedly, intermittent use rather than continuous therapy be considered [45]. An additional strategy to lower the cardiovascular risk is co-administration of low-dose aspirin (ASA). Aspirin's antiplatelet effect may offset the pro-thrombotic potential of COX-2 inhibition, particularly in high-risk patients. Although the interaction with selective COX-2 inhibitors such as celecoxib may modestly reduce aspirin's effect at standard therapeutic doses, this does not appear to translate into higher cardiovascular event rates. When considering use of aspirin with COX-2 inhibitors, practitioners should note that the gastrointestinal safety advantage of the COX-2-selective drug is diminished, so addition of a proton-pump inhibitor should be considered to prevent upper-GI complications [15,45]. Table 3 summarizes main cardiovascular effects, associated doses, and absolute risks.

Table 2. Mechanisms involved in cardiovascular effects of COX-2 inhibitors.

Category	Specific Mechanism	Physiological or Molecular Alteration	Associated Cardiovascular Effects
Prothrombotic	↓ Prostacyclin	↓ Vasodilation	↑ Prothrombotic state
	↑ Thromboxane A2.	↑ Platelet aggregation	Vascular damage
	↓ Thrombomodulin	↑ FVa and FVIIIa	Impaired protein C activation
	↓ PPARδ	Expression of FT Activation of coagulation cascade	Thrombosis

Table 2. Cont.

Category	Specific Mechanism	Physiological or Molecular Alteration	Associated Cardiovascular Effects
Renal	↓ Prostaglandins ↓ Prostacyclins	Infiltration of proinflammatory cells at the kidney ↓ Natriuresis	Edema Arterial hypertension Heart failure ↑ Peripheral vascular resistance
	↑ ADMA and L-NMMA	↓ Systemic nitric oxide.	↑ Arterial hypertension Vascular damage
	↑ Vasopressor effect of angiotensin-2	↓ Renal medullary blood flow	Edema Arterial hypertension
	↓ Aldosterone glucuronidation	↑ Aldosterone	Arterial hypertension Water and sodium retention
Genetic and Molecular	↑ MMP-1, MMP-3	Plaque rupture Vascular damage Tissue destruction	Coronary heart disease Prothrombotic
	↑ IL-8	↑ Metalloproteinase expression	Coronary heart disease Prothrombotic
Peripheral Nervous System	VEGFA	↓ Decrease in NOS Vasoconstriction Vascular damage	Arterial hypertension Prothrombotic Coronary heart disease
	MMP-9	VEGFA decreased	Arterial hypertension Prothrombotic
	BRCA1	↑ Migration of smooth muscle cells in the carotid muscle.	Coronary heart disease
	CACNA1E	Alteration of voltage-gated calcium channels in blood vessels and myocardium	Arterial hypertension CVD
	C-reactive protein in the 3' untranslated region	Atherosclerosis	Arterial hypertension
	Genotipo CYP2C9	↓ Clearance of coxibs	Metabolic syndrome Coronary heart disease
	Crosstalk	Cardiomyocyte DNA damage Apoptosis, necrosis	Increased cardiovascular adverse effects Heart failure
	↑ Caspase-3, Mcl-1, Bax and Bcl-2	Cardiac apoptosis	Cardiac injury
	Profibrotic	Cardiac fibrosis	CVD
	↑ 20-hydroxyeicosatetraenoic acid		Increased cardiac enzymes
	↑ Endothelin-1	Vasoconstriction	Arterial hypertension
	↑ Brain natriuretic peptide		Coronary heart disease

↑—Increased; ↓—Decreased; FVa—Coagulation factor V; FVIII—Cardiovascular disease II; PPARδ—Peroxisomal proliferator activated receptor δ; ADMA—Asymmetric dimethylarginine; FT—Tissue factor; L-NMMA—Monomethyl-L-arginine; MMP-1—Matrix metalloproteinase-1; MMP-3—Matrix metalloproteinase-3; IL-8—Interleukin -8; VEGFA—Vascular endothelial growth factor “A”; MMP-9—Matrix metalloproteinase-9; BRCA1—Estrogen resistance protein 1 of cancer of breast; CVD—Cardiovascular disease; CACNA1E—Calcium channel alpha subunit E1.

Table 3. Doses and absolute risks associated with cardiovascular effects of COX-2 inhibitors.

Drug	Associated Dose	Main Cardiovascular Effect	Key Clinical Study (Design/Population)	RR or HR (95% CI)	Conclusion	Absolute Risk	Reference
Rofecoxib	25–50 mg/day	↑ AMI and major thrombotic events	VIGOR (2000, RA, 8076 patients, active-controlled RCT vs. naproxen); APPROVe (2005, adenoma prevention, 2586 patients, placebo-controlled RCT)	VIGOR: $\approx 5 \times$ ↑ AMI risk; APPROVe: RR 1.92 (1.19–3.11)	Demonstrated the highest thrombotic CVR among all coxibs; withdrawn from the market in 2004	$\approx 1/100$	[10,13]
Celecoxib	200–400 mg BID	↑ CVR at high doses (CV death, AMI, CVE); neutral at low/moderate doses	APC (2005, adenoma prevention, placebo-controlled RCT); PRECISION study (2016, OA/RA, non-inferiority RCT vs. ibuprofen and naproxen)	APC: HR 2.6–3.4; PRECISION: HR 0.93 (0.76–1.13) vs. naproxen	Dose-dependent CVR. Doses ≤ 200 mg/day considered safe in patients without pre-existing CVD	$\approx 0.8/100$	[15,16]
Etoricoxib	60–90 mg/day	Thrombotic risk comparable to diclofenac	MEDAL (2006, OA/RA, >34,000 patients, non-inferiority RCT vs. diclofenac)	HR 0.95 (0.81–1.11)	Did not significantly increase risk vs. diclofenac, but both higher than placebo	$\approx 1.2/100$	[48]
Valdecoxib	20–40 mg BID (after parecoxib 40 mg IV BID)	↑ AMI, cardiac arrest, CVE, and pulmonary embolism after CABG surgery	Nussmeier et al. 2005 (post-CABG, double-blind RCT, 1671 patients)	RR 3.7 (1.0–13.5)	Very high CVR in post-cardiac surgery patients; withdrawn from market in 2005	$\approx 1.5/100$	[49]
Parecoxib	40 mg IV BID (followed by oral valdecoxib)	↑ Serious CV events in post-cardiac surgery patients	Nussmeier et al. 2005 (same post-CABG trial)	RR ≈ 3.7	Pro-drug of valdecoxib; similar CVR in perioperative settings; withdrawn in 2005	$\approx 1.5/100$	[49]
Lumiracoxib	400 mg/day	Arterial thrombosis like traditional NSAIDs	TARGET (2004, OA, 18,325 patients, active-controlled RCT vs. naproxen/ibuprofen)	RR ≈ 1.0 (NS)	No significant increase in CVR; withdrawn for hepatotoxicity	$\approx 0.10/100$	[50]
COXIBS (combined analysis)	—	↑ Major cardiovascular events vs. placebo	CNT Collaboration (2013, meta-analysis, 280,000 participants)	RR 1.37 (1.14–1.66)	Overall ↑ average CVR, especially in patients with pre-existing CVD	$\approx 0.3/100$	[18]

ADMA—Asymmetric dimethylarginine; AMI—Myocardial infarction; APC—Adenoma Prevention with Celecoxib; APPROVe—Adenomatous Polyp Prevention on Vioxx; COX-2—Cyclooxygenase-2; COXIBS—COX-2 inhibitors; CVE—Cerebrovascular events; CVR—Cardiovascular risk; MMP-1—Matrix metalloproteinase-1; MMP-3—Matrix metalloproteinase-3; MMP-9—Matrix metalloproteinase-9; NSAIDs—Nonsteroidal anti-inflammatory drugs; PPAR δ —Peroxisomal proliferator-activated receptor δ ; PRECISION study—Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen; PRECISION-ABPM—Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen Ambulatory Blood Pressure Measurement; PTGS1—Prostaglandin-endoperoxide synthase-1; SNP—Single nucleotide polymorphism; VEGFA—Vascular endothelial growth factor “A”; VIGOR—Vioxx and Gastrointestinal Outcomes Research.

7. Conclusions

Coxibs came into existence in 1990 with the sole purpose of producing an anti-inflammatory effect without gastrointestinal or renal side effects [4,6]. However, multiple studies have now confirmed that, despite their anti-inflammatory effect, coxibs may increase cardiovascular side effects. The inhibition of COX-2 by coxibs is strongly linked to prothrombotic, renal, molecular, and genetic mechanisms which translate into an increased prothrombotic state, sodium and water retention, vasoconstriction increase and vasodilation decrease, vascular damage, direct harm to the myocardium, cell death, and cardiac fibrosis. These increase the cardiovascular risks of systemic arterial hypertension, heart infarction, stroke, and sudden death. The cardiovascular-related risks posed by coxibs are often overlooked in medical practice; these drugs are commonly prescribed for pain, with a focus on gastric and renal protection, without considering potential cardiovascular damage in patients who already have risk factors for cardiovascular diseases. We hope that this review encourages further reflection on the adverse effects of coxibs, so that the potential harm a patient might undergo when prescribed them is considered.

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Abbreviations

The following abbreviations are used in this manuscript:

ADMA	Asymmetric dimethylarginine
AMI	Myocardial infarction
APC	Adenoma Prevention with Celecoxib
APPROVe	Adenomatous Polyp Prevention on Vioxx
CACNA1E	Calcium channel alpha subunit E1
COX-2	Cyclooxygenase-2
COXIBS	COX-2 inhibitors
CVE	Cerebrovascular events
CVR	Cardiovascular risk
FT	Factor expression
L-NMMA	Monomethyl-L-arginine
MMP-1	Matrix metalloproteinase-1
MMP-3	Matrix metalloproteinase
MMP-9	Matrix metalloproteinase
NSAIDs	Nonsteroidal anti-inflammatory drugs
PPAR δ	Peroxisomal proliferator activated receptor δ
PRECISION study	Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen

PRECISION-ABPM	Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen Ambulatory Blood Pressure Measurement.
PTGS1	Prostaglandin-endoperoxide Synthase-1
SNP	Single nucleotide polymorphisms
VEGFA	Vascular endothelial growth factor “A”
VIGOR	Vioxx and Gastrointestinal Outcomes Research

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