REVIEW

Cardiovascular effects of cyclooxygenase-2 inhibitors: a mechanistic and clinical perspective

Correspondence Professor Carlo Patrono MD, FRCP, Istituto di Farmacologia, Università Cattolica del S. Cuore, Largo Francesco Vito, 1, 00168 Rome, Italy. Tel.: +39 06 3015 4253; Fax: +39 06 305 0159; E-mail: carlo.patrono@rm.unicatt.it

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Carlo Patrono

Department of Pharmacology, Catholic University School of Medicine, Rome, Italy

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Prostaglandin (PG) H synthase 2 [also referred to colloquially as cyclooxygenase (COX) 2] represents a key enzyme in arachidonic acid metabolism in health and disease. It is both constitutively expressed in several human tissues (e.g. kidney and brain) and induced in various cell types (including monocytes/macrophages, vascular endothelial cells and colorectal cancer cells) in response to inflammatory cytokines, laminar shear stress and growth factors. Products of COX-2 activity (e.g. PGE₂ and prostacyclin) are involved in diverse physiological and pathophysiological processes, including renal haemodynamics and the control of blood pressure, endothelial thromboresistance, pain and inflammation, and colorectal tumorigenesis. Therefore, it is not surprising that COX-2 inhibitors display multifaceted clinical effects, ranging from reduced pain and inflammation to increased blood pressure, an increased risk of atherothrombotic events and a decreased risk of colorectal cancer. The aim of the present article was to review the cardiovascular effects of COX-2 inhibitors [traditional nonsteroidal anti-inflammatory drugs (tNSAIDs) and coxibs alike], with a focus on the mechanisms contributing to the clinical readouts of COX-2 inhibition.

Prostaglandin (PG) H synthase 2 [also referred to colloquially as cyclooxygenase (COX) 2] represents a key enzyme in arachidonic acid metabolism in health and disease [1]. It is both constitutively expressed in several human tissues (e.g. kidney and brain) and induced in various cell types (including monocytes/macrophages, vascular endothelial cells and colorectal cancer cells) in response to inflammatory cytokines, laminar shear stress and growth factors [2, 3]. Products of COX-2 activity [e.g. PGE₂ and prostacyclin (PGI₂)] are involved in diverse physiological and pathophysiological processes, including renal haemodynamics and the control of blood pressure, endothelial thromboresistance, pain and inflammation, and colorectal tumorigenesis [4, 5]. Therefore, it is not surprising that COX-2 inhibitors display multifaceted clinical effects, ranging from reduced pain and inflammation [4] to increased blood pressure [6], an increased risk of atherothrombotic events [7] and a decreased risk of colorectal

cancer [5]. The aim of the present article was to review the cardiovascular effects of COX-2 inhibitors [traditional nonsteroidal anti-inflammatory drugs (tNSAIDs) and coxibs alike], with a focus on the mechanisms contributing to the clinical readouts of COX-2 inhibition.

Inhibition of COX-1 and COX-2: COX isozyme selectivity as a continuous variable

All NSAIDs can inhibit COX-1 and COX-2 *in vitro* in a concentration-dependent fashion. The ratio between the 50% inhibitory concentration (IC₅₀) values for COX-1 and COX-2 has been used to describe the variable COX-2 selectivity of these agents and, based on largely arbitrary thresholds,

to characterize 'selective' vs. 'nonselective' inhibitors [8]. A widely used method to characterize the COX isozyme selectivity of NSAIDs is represented by whole-blood assays of COX-1 [9] and COX-2 [10] activities that exploit the constitutive and lipopolysaccharide (LPS)-inducible COX activities of circulating platelets and monocytes, as reflected by serum thromboxane (TX) B₂ and plasma PGE₂ levels, respectively. Figure 1 describes the IC₅₀ values for COX-1 vs. COX-2 inhibition of 10 different tNSAIDs and five coxibs, as determined by the same whole-blood assays [11]. These analyses established three important points: (i) COX-2 selectivity is a continuous variable that does not justify a dichotomous definition of 'selective' and 'nonselective' COX-2 inhibitors; (ii) even a highly selective COX-2 inhibitor (e.g. etoricoxib or lumiracoxib) can inhibit COX-1 at sufficiently high concentrations, thus COX-2 selectivity is a relative rather than an absolute feature of coxibs; (iii) there is substantial overlap between the COX isozyme selectivity of some tNSAIDs (e.g. diclofenac and nimesulide) and a first-generation coxib (i.e. celecoxib) [11]. The same whole-blood assays can be applied *ex vivo* to monitoring the extent and duration of platelet COX-1 and monocyte COX-2 inhibition following oral dosing with the inhibitor [12–16]. These human studies showed substantial interindividual variability in the extent of COX isozyme inhibition both by tNSAIDs and coxibs, which could only partially be explained by pharmacokinetic variability [13, 14]. Moreover, they demonstrated partial inhibition of platelet COX-1 by therapeutic doses of allegedly 'selective' COX-2 inhibitors [12–14].

Figure 1

Cyclooxygenase (COX) 2 selectivity as a continuous variable. Concentrations of various COX-2 inhibitors to inhibit the activity of platelet COX-1 and monocyte COX-2 by 50% (IC₅₀) are plotted on the abscissa and ordinate scales, respectively. The solid line describes equipotent inhibition of both COX-1 and COX-2. Symbols to the left of this line denote greater inhibition of COX-1 than COX-2. Symbols to the right of this line indicate progressively greater inhibition of COX-2 than COX-1 – i.e. increasing degrees of COX-2 selectivity. 6-MNA, 6-methoxy-2-naphthylacetic acid, the active metabolite of nabumetone. Data updated from FitzGerald *et al.* [11]

From the assessment of prostanoid biosynthetic capacity *ex vivo* to evaluation of prostanoid biosynthesis and inhibition *in vivo*

It should be emphasized that the COX-1 and COX-2 whole-blood assays give an indication of the maximal prostanoid production by circulating blood cells when challenged in a test tube by endogenously formed thrombin or exogenously added LPS, respectively [9, 10]. Although the reduction in platelet TXB₂ and monocyte PGE₂ production can accurately reflect the degree of inhibition of COX isozymes by blood levels of the inhibitor, these measurements by no means reflect the actual rate of prostanoid biosynthesis and inhibition *in vivo*. The relationship between inhibition of COX activity *ex vivo* and the reduction in prostanoid biosynthesis *in vivo* is not necessarily linear [17, 18], thus making prediction of the latter based on assessment of the former a questionable exercise. In fact, the relationship between inhibition of platelet COX-1 activity, as reflected by serum TXB₂, and the reduction in TXA₂ biosynthesis, as reflected by urinary 11-dehydro-TXB₂ (TXM) excretion, is strikingly nonlinear [17, 18], whereby 97–100% suppression of the former is necessary to produce 50–80% reduction of the latter (Figure 2). By contrast, there is a linear relationship between inhibition of monocyte COX-2 activity, as reflected by LPS-induced PGE₂ production, and the reduction in PGI₂ biosynthesis, as reflected by urinary 2,3-dinor-6-keto-PGF_{1α} (PGIM) [19]

Figure 2

Nonlinear relationship between inhibition of serum thromboxane B₂ (TXB₂) and urinary 11-dehydro-thromboxane B₂ (TXM). Individual percentage inhibition values are depicted in the upper panel from all on-treatment and post-treatment measurements. The lower panel is a simulated detail of the upper panel. Reproduced from Santilli *et al.* [18], with permission from the American College of Cardiology

(Figure 3). All tNSAIDs and coxibs that have been studied with this methodology achieve 75–95% inhibition of COX-2 activity at therapeutic plasma concentrations [19], a level of inhibition found to reduce PGIM excretion by 50–80% [14–16, 20]. Depending on COX-2 selectivity and daily dose, tNSAIDs and coxibs achieve variable degrees of COX-1 inhibition at therapeutic plasma concentrations, ranging from 10% (e.g. rofecoxib and etoricoxib) to 95% (high-dose naproxen) [19]. Because of the nonlinear relationship depicted in Figure 2, only high-dose naproxen (500 mg b.i.d.) can be expected to produce an aspirin-like effect on TXA₂-dependent platelet activation *in vivo*, as shown by comparable suppression of TXM excretion throughout the dosing interval [16]. By contrast, all other tNSAIDs and coxibs would be expected to produce a trivial-to-modest reduction in platelet activation *in vivo* because of incomplete suppression of COX-1 activity [19]. Thus, although biochemical COX-2 selectivity (as depicted in Figure 1) is clearly a continuous variable [11], functional COX-2 selectivity (i.e. selective sparing of COX-1-dependent platelet function) is a shared feature of most tNSAIDs (with the notable exception of high-dose naproxen) and coxibs because they all inhibit platelet COX-1 in the nonfunctional range (i.e. <95%).

Measurements of urinary TXM excretion have been used extensively to characterize platelet activation in a variety of clinical settings, including acute coronary syndromes [21, 22], acute ischaemic stroke [23, 24], myeloproliferative neoplasms [25], and type 1 [26, 27] and type 2 [28] diabetes mellitus, and in association with several cardiovascular risk factors [29]. Similarly, measurements of urinary PGIM have been used to characterize the homeostatic response of endothelial PGI₂ biosynthesis to transient [21] or persistent [20, 27, 30, 31] platelet activation. However, human studies suffer from inherent limitations in assessing the precise cellular source(s) of urinary prostanoid metabolites. A study in healthy subjects has reported an approximately 80%

Figure 3

Linear relationship between inhibition of human whole-blood cyclooxygenase (COX) 2 activity [i.e. lipopolysaccharide-induced prostaglandin (PG)E₂] *ex vivo* and inhibition of 2,3-dinor-6-keto-PGF_{1α} (PGIM) (i.e. urinary levels of PGIM, a major enzymatic metabolite of prostacyclin, mostly COX-2-derived) *in vivo* after oral dosing with aspirin 100 mg daily, naproxen sodium 220 mg b.i.d., etoricoxib 90 mg daily, rofecoxib 25 mg daily and celecoxib 200 mg b.i.d. Reproduced from García Rodríguez *et al.* [19], with permission from the American College of Cardiology. ● Aspirin 100 mg o.d., ▼ Etoricoxib 90 mg o.d., ◆ Rofecoxib 25 mg o.d., ● Celecoxib 200 mg b.i.d., ■ Naproxen 220 mg b.i.d.

reduction in urinary TXM excretion following one-week administration of aspirin 100 mg daily or naproxen 500 mg b.i.d. [16], thus suggesting that platelet COX-1 activity is a major source of TXA₂ biosynthesis and TXM excretion. However, extraplatelet sources of TXA₂ production, such as the kidney [32] and COX-2-expressing inflammatory cells [33], may also contribute to TXM excretion. Similarly, the involvement of COX-2 in PGI₂ biosynthesis and PGIM excretion has been inferred by short-term intervention studies demonstrating a comparable reduction in urinary PGIM with structurally unrelated COX-2 inhibitors, such as nimesulide [20], celecoxib [14], rofecoxib [15] or naproxen [16], regardless of their variable COX isozyme selectivity, but not with aspirin 100 mg daily [16, 19, 27, 31]. The contribution of endothelial COX-1 to physiological PGI₂ production [34] remains to be demonstrated in humans [35].

Deletion of COX-2 in the mouse vasculature reduces the urinary excretion of PGIM, but not TXM, and predisposes the animals to both hypertension and thrombosis [36]. These findings are consistent with COX-2 being the major source of PGI₂ biosynthesis and metabolism to PGIM, as suggested by the human pharmacology of COX-2 inhibitors [14–16, 20]. Furthermore, the clinical phenotype of vascular COX-2 deletion is consistent with PGI₂ playing a physiological role in endothelial thromboresistance and blood pressure control [37], a concept supported by the thrombogenic phenotype associated with deletion of the gene encoding the PGI₂ IP receptor [38]. Subsequent experiments revealed that IP deletion predisposed to thrombosis in a gene dose-dependent fashion; the effect of a COX-2 inhibitor in thrombosis models was intermediate between *IP*^{+/-} and *IP*^{-/-} mice [39].

Functional readouts of COX-isozyme inhibition in the cardiovascular system

Although experimental studies in murine models of cardiovascular disease have established that inhibition of COX-2-derived PGI₂ removes a protective restraint on thrombogenesis, hypertension and atherogenesis *in vivo* [39], characterization of the functional consequences of COX-2 inhibition in humans has been problematic and generated many controversial findings. Endothelium-dependent, flow-mediated dilation (FMD) of the brachial artery has been used to assess the effects of COX-2 inhibitors on endothelial function [40–42]. While two independent studies have reported an increase in FMD following 1- to 2-week treatment with celecoxib 200 mg b.i.d. in hypertensive [40] and coronary artery disease [41] patients, a 2-week course of either indomethacin (75 mg b.i.d.) or rofecoxib (12.5 mg bid) failed to improve FMD in patients with rheumatoid arthritis [42]. It has been clearly shown that both tNSAIDs and coxibs increase blood pressure in hypertensive and normotensive individuals, and interfere with the blood pressure-lowering effect of antihypertensive treatment [43–45]. This is also true for high-dose paracetamol [46], a weak COX-2 inhibitor with modest COX-2 selectivity (Figure 1). By contrast, low-dose aspirin (75 mg daily) did not affect blood pressure control or the need for antihypertensive therapy in intensively treated hypertensive patients [47]. Moreover, low-dose aspirin did not affect renal

function in patients with type-2 diabetes mellitus [48], consistent with its lack of effect on COX-2-dependent renal prostanoid production in healthy subjects [49] and patients with renal disease [50]. Overall, these findings suggest that all COX-2 inhibitors (including high-dose aspirin) impair blood pressure control through systemic as well as renal COX-2-dependent effects [11]. These include sodium and water retention and increased vasoconstriction. Although early studies had suggested that celecoxib was less likely than rofecoxib to raise blood pressure [51], the design of these studies often failed to address the comparability of the two drug regimens in terms of the extent and duration of COX-2 inhibition.

In contrast to the easily measurable haemodynamic and renal effects resulting from inhibition of COX-2-dependent PGI₂ biosynthesis, the platelet readout of COX-2 inhibition remains elusive because of artifactual platelet activation during and after blood sampling, and because of the partial contribution of COX-2 to TXM excretion in clinical settings associated with platelet activation, such as cigarette smoking [33] and essential thrombocythemia [52].

In mice, vascular disruption of COX-2 depressed expression of endothelial nitric oxide (NO) synthase (eNOS) and the consequent release and function of NO [36]. Furthermore, a PGI₂ analogue rescued both the defect in eNOS expression *in vitro* and the hypertensive phenotype *in vivo* in the mutant mice [36]. COX-2^{-/-} mice had increased plasma levels of the endogenous NOS inhibitors, asymmetrical dimethylarginine (ADMA) and monomethyl-L-arginine, and reduced endothelial NO responses [53]. In healthy subjects, one-week treatment with celecoxib 200 mg b.i.d. or naproxen 500 mg b.i.d. similarly increased plasma levels of ADMA by approximately 20% [53]. However, the functional significance of these modest biochemical changes remains to be determined.

Serious vascular readouts of COX-2 inhibition

Based on the biochemical and functional evidence reviewed above, one could anticipate that both transient increases in platelet activation at sites of fissured or ruptured atherosclerotic plaques and prolonged increases in blood pressure could contribute to untoward cardiovascular consequences of COX-2 inhibition, reflecting the physiological antiplatelet and vasodilator actions of vascular PGI₂, respectively [29]. A prevalence of the platelet mechanism would be expected to translate into early appearance of a coronary hazard, while prevalence of the blood pressure mechanism would predict longer-term increases in cerebrovascular hazard. Moreover, the prothrombotic consequences of COX-2 inhibition would be expected to be attenuated by persistent, high-grade suppression of platelet COX-1 activity – a feature of aspirin and high-dose naproxen – while concomitant platelet inhibition would not be expected to influence the long-term consequences of increased blood pressure. In addition, while lower degrees of COX-1 inhibition in epithelial cells of the gastrointestinal (GI) mucosa would plausibly predict a lower burden of serious GI complications associated with coxibs

vs. tNSAIDs, anything less than persistent 95% inhibition of platelet COX-1 would not be expected to affect the burden of serious vascular complications because the nonlinear relationship depicted in Figure 2 markedly restrains the potential influence of COX-2 selectivity on platelet activation *in vivo* [6, 8]. Given these premises, how do the results of randomized controlled trials (RCTs) of COX-2 inhibitors fit with the theoretical expectations? In answering this question, I shall rely primarily on the results of individual participant data (IPD) meta-analyses of all the published and unpublished RCTs of any NSAID vs. placebo or any NSAID vs. another comparator NSAID(s) performed by the Coxib and traditional NSAID Trialists' (CNT) Collaboration [7]. It should be emphasized that, with one notable exception [54], none of the NSAID RCTs had serious vascular events as the primary endpoint, thus reinforcing the need to examine the totality of the evidence rather than individual studies. Moreover, the CNT meta-analyses largely relied on the much larger and longer trials of coxibs vs. placebo and coxibs vs. one or two tNSAIDs, as the largest RCT of a tNSAID vs. placebo involved only a few hundred patients treated for a few months, thus providing negligible information on serious vascular outcomes [7]. Therefore, rate ratios for the comparison tNSAID vs. placebo were obtained by combining estimates obtained directly (from the small number of trials including such a comparison) with estimates obtained indirectly (from a comparison of trials of coxib vs. tNSAID with trials of coxib vs. placebo).

Overall, the main findings of the CNT meta-analyses are consistent with the theoretical expectations outlined above and with the most widely accepted mechanistic interpretation of the cardiovascular hazard associated with COX-2 inhibitors [6, 8, 39]. One important limitation of these analyses is represented by the fact that only three tNSAIDs – i.e. diclofenac, ibuprofen, and naproxen – were used as comparators in the coxib trials, and that only high-dose regimens of any NSAID were investigated adequately in these trials. Thus, we lack reliable information on other currently available tNSAIDs or on the cardiovascular safety of lower-dose regimens of NSAID therapy. An increased risk of major vascular events appeared early, as detected in short-term trials of 10-day coxib therapy vs. placebo following coronary artery bypass surgery [55], and disappeared slowly, as shown by long-term RCTs [56]. Major vascular events (nonfatal myocardial infarction, nonfatal stroke, or vascular death) were increased by about 40% by a coxib or diclofenac, chiefly because of a 75% increase in major coronary events; the rate ratios of celecoxib and rofecoxib vs. placebo were virtually identical, with no statistical heterogeneity in risk estimates among five different coxibs; ibuprofen had a similar – although not statistically significant – impact on major vascular events, and also significantly doubled the risk of major coronary events; naproxen did not significantly increase the risk of major vascular or coronary events [7]. There was no detectable increase in stroke with any NSAID, although the wide 95% confidence interval of the point estimates cannot exclude a moderate treatment effect. Vascular death was increased significantly by about 60% by coxibs and diclofenac, nonsignificantly by ibuprofen, but not by naproxen [7]. The proportional effects on major vascular events were independent of baseline characteristics, including vascular risk;

therefore, the absolute excess caused by NSAID therapy was directly proportional to the baseline vascular risk of the patients. Heart failure risk was roughly doubled by all NSAIDs [7].

The pattern of the serious cardiovascular effects of COX-2 inhibitors is consistent with the increased risk of coronary events (largely atherothrombotic in nature) being related to a diminished restraining effect of endothelial PGI₂ on platelet activation at sites of plaque rupture or fissuring [21, 22, 29], as suggested by in-depth studies of experimental thrombogenesis in COX-2-deficient mice [36, 39] (Figure 4). The early appearance of increased risk would not be explained by a restraining effect of PGI₂ on atherogenesis demonstrated in murine models of vascular disease [36, 39], although the latter mechanism might contribute to long-term changes in cardiovascular risk. A major contribution of increased blood pressure would be difficult to reconcile with the time-frame of increased vascular risk, as well as with the apparent lack of increase in stroke risk [7]. Moreover, the neutral atherothrombotic phenotype associated with high-dose naproxen, in contrast to high-dose regimens of diclofenac and ibuprofen, suggests that keeping an adequate brake on platelet COX-1 throughout the 12-hour dosing interval may attenuate the serious vascular consequences of PGI₂ inhibition [29]. This interpretation of the naproxen findings seems biologically plausible because COX-1 knockdown in mice attenuates the prothrombotic effect of COX-2 inhibition [39]. In this context, it should be emphasized that the cardiovascular phenotype of low-dose aspirin in primary prevention RCTs – i.e. in asymptomatic subjects at relatively low vascular risk comparable with the patients enrolled in the coxib RCTs – is represented by a reduced risk of major coronary

events with no apparent change in stroke risk [57], consistent with TXA₂-dependent platelet activation playing a more important role in coronary than in cerebrovascular atherothrombotic events [29]. Moreover, profound and sustained suppression of platelet COX-1 protects high-risk patients from the untoward vascular consequences of COX-2 inhibition by high doses of aspirin [58]. Finally, the finding that both tNSAIDs and coxibs doubled the risk of heart failure, causing hospital admission, is consistent with this being a COX-2-dependent hazard that is unrelated to variable platelet COX-1 inhibition, as would be expected from a serious complication most likely related to the haemodynamic consequences of COX-2 inhibition in the kidney and systemic vasculature [6, 7] (Figure 4). However, selective COX-2 deletion in cardiomyocytes results in mild heart failure and a predisposition to arrhythmogenesis in mice [59]. Thus, in addition to causing volume expansion and increased blood pressure, COX-2 inhibitors may have direct cardiac effects contributing to an increased risk of heart failure (Figure 4).

Conclusions and perspective

Up until 1999, GI toxicity represented the main safety concern of NSAID therapy [60]. The clinical development of coxibs specifically addressed this concern, and demonstrated the improved GI safety of highly selective COX-2 inhibitors vs. tNSAIDs based on large outcome studies and their meta-analysis [7]. However, basic research and clinical studies originally triggered by a red flag of a potential cardiovascular safety issue with celecoxib [14] and rofecoxib

Figure 4

Mechanisms contributing to the cardiovascular effects of cyclooxygenase (COX) 2 inhibitors. The figure depicts the consequences of COX-2 inhibition in the vasculature, the heart and the kidney, and its short- and long-term clinical readouts. CV, cardiovascular; GFR, glomerular filtration rate; NO, nitric oxide; PG, prostaglandin; RBF, renal blood flow

[15] have illuminated an area of cardiovascular toxicity that had remained outside the radar of observational studies [61]. The CNT meta-analyses of NSAID RCTs have now clearly demonstrated that, although the relative risk of serious GI complications is substantially higher than the corresponding value for serious vascular events, the absolute excess of the two is fairly comparable and the latter carry a higher risk of short-term mortality and long-term disability than the former [7]. These analyses have also established that the increased risk of atherothrombotic complications represents a mechanism-based class effect of COX-2 inhibitors, regardless of COX isozyme selectivity [7]. Therefore, it would be safe to assume that any COX-2-inhibiting drug regimen may share this effect until convincingly proven otherwise. Thus, although a high-dose naproxen regimen does not appear to increase vascular events in low-risk subjects not taking aspirin [7], the same pattern of cardiovascular safety should not be extrapolated to a low-dose regimen that only incompletely blocks platelet COX-1 activity [62] or to a high-dose regimen administered to aspirin-treated patients because of a potential pharmacodynamic interaction with low-dose aspirin [63, 64].

The CNT analyses did not provide any evidence that the effect of coxibs on the risk of major vascular events is attenuated by concomitant aspirin use at baseline [7], as would be expected based on the mechanistic considerations discussed in the present review. However, because there was substantial underrepresentation of aspirin-treated participants in the coxib trials, this analysis lacked statistical power to assess reliably whether the vascular hazards of a coxib were modified by concomitant low-dose aspirin therapy (or other antiplatelet regimens) [6]. The ongoing Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION) trial [65], a randomized, double-blind, parallel-group study of cardiovascular safety in approximately 20 000 osteoarthritis or rheumatoid arthritis patients with, or at, a high risk for cardiovascular disease comparing celecoxib with naproxen and ibuprofen is investigating a largely aspirin-treated population at higher vascular risk than in the previous coxib trials [7]. Both the non-inferiority design of PRECISION and the potential for a differential drug-drug interaction between both tNSAIDs and low-dose aspirin [63, 64], but not between celecoxib and low-dose aspirin [64, 66], will make interpretation of its results problematic at best.

The coxib experience, as well as the Food and Drug Administration's decision not to approve etoricoxib for marketing in the USA, has discouraged drug companies from developing novel NSAIDs with the aim of reducing the cardiovascular hazard associated with currently available agents. A promising class of inhibitors of microsomal PGE-synthase1 (mPGES-1) has been developed during the last 10 years but it is unclear whether any will actually enter phase III trials. Deletion of mPGES-1 in the vasculature and myeloid cells differentially modulates the response to vascular injury, implicating macrophage mPGES-1 as a cardiovascular drug target [67].

While the role of COX-2 in colorectal cancerogenesis had raised hopes for a chemopreventive effect of COX-2 inhibitors [68], long-term administration of these agents actually demonstrated their cardiovascular hazard, limiting any further investigation of their anticancer effects. However,

COX-inhibition by low-dose aspirin appears to confer protection against colorectal (and other) cancer and is currently being investigated as a potential adjuvant therapy in different oncological settings [69].

Finally, in light of the substantial interindividual variability in response to COX-2 inhibitors affecting both clinical efficacy and safety [70], research efforts should be focused on developing biomarkers that enhance the therapeutic response to COX-2 inhibition and identify patients at higher risk of its untoward cardiovascular consequences.

Competing Interest

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; CP received personal fees from AstraZeneca, personal fees from Bayer, an institutional grant from Bayer and personal fees from the Aspirin Foundation, in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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