Arteriosclerosis, Thrombosis, and Vascular Biology

REVIEW

Prostanoids in Cardiac and Vascular Remodeling

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ABSTRACT: Prostanoids are biologically active lipids generated from arachidonic acid by the action of the COX (cyclooxygenase) isozymes. NSAIDs, which reduce the biosynthesis of prostanoids by inhibiting COX activity, are effective anti-inflammatory, antipyretic, and analgesic drugs. However, their use is limited by cardiovascular adverse effects, including myocardial infarction, stroke, hypertension, and heart failure. While it is well established that NSAIDs increase the risk of atherothrombotic events and hypertension by suppressing vasoprotective prostanoids, less is known about the link between NSAIDs and heart failure risk. Current evidence indicates that NSAIDs may increase the risk for heart failure by promoting adverse myocardial and vascular remodeling. Indeed, prostanoids play an important role in modulating structural and functional changes occurring in the myocardium and in the vasculature in response to physiological and pathological stimuli. This review will summarize current knowledge of the role of the different prostanoids in myocardial and vascular remodeling and explore how maladaptive remodeling can be counteracted by targeting specific prostanoids.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: heart failure ■ hypertension ■ myocardial infarction ■ prostaglandins ■ vascular remodeling

Prostanoids are bioactive lipid mediators that act locally to mediate a diverse range of physiological and pathological processes.[1,2] They are oxygenated metabolites derived from arachidonic acid (AA), a 20-carbon polyunsaturated omega-6 (n-6) fatty acid. Free AA is metabolized by the sequential actions of prostaglandin (PG)G/H synthase, also known as COX (cyclooxygenase), isomerases, and synthases. This results in the formation of prostanoids, including PGs, prostacyclin (PGI_2), and thromboxane A_2 (TxA_2; Figure) .[3]

COX-1 and COX-2 activity are inhibited by traditional NSAIDs, like ibuprofen, naproxen, and diclofenac and NSAIDs purposely designed to inhibit COX-2 (coxibs), such as rofecoxib, celecoxib, and valdecoxib (Figure).

Despite NSAIDs' efficacy in relieving pain and inflammation,[4] their use is limited by rare but serious adverse events, including cardiovascular complications (eg, myocardial infarction [MI], stroke, hypertension, and heart failure [HF]).[5–9] In addition to the suppression of COX-2–derived vasoprotective prostanoids that may increase the risk for atherothrombotic events and hypertension, NSAIDs may increase the risk for HF by impairing cardiovascular remodeling after ischemic and nonischemic events. In response to a physiological (pregnancy, exercise, etc) or pathological stimulus (ischemic event, pressure or volume overload, hemodynamic stress, etc), the heart and the vasculature undergo adaptive remodeling as part of the healing process.[10] The cellular, molecular, and interstitial events associated with the adaptive remodeling determine changes in the size, mass, geometry, and function of the heart and the vasculature. In contrast to adaptive remodeling, maladaptive remodeling occurs when the response is excessive and uncontrolled. Clinical consequences of maladaptive remodeling include cardiac dysfunction, cardiac fibrosis and hypertrophy, arrhythmia, atherosclerosis, aneurysm formation, vascular hyperplasia, and stiffness.[10] Many molecular mechanisms and, therefore, several potential molecular mediators are involved in this process, including inflammatory mediators, reactive oxygen species, mitochondrial metabolites, energy metabolites, contractile proteins, neurohormonal mediators, calcium handling proteins, and collagen fibers.[10] The exact role of these mediators and the magnitude of their relative contribution remains to be established. Among the inflammatory mediators, prostanoids contribute to adverse remodeling by modulating the structural and functional changes occurring in the myocardium or vasculature in response to ischemic or nonischemic events. In this review, we will

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Arterioscler Thromb Vasc Biol is available at www.ahajournals.org/journal/atvb

Nonstandard Abbreviations and Acronyms

AA	arachidonic acid
AAA	aortic aneurysm
AKR1C3	aldo-keto reductase family 1 member C3
Ang II	angiotensin II
ANP	atrial natriuretic peptide
BP	blood pressure
CM-Cox-2 KO	cardiomyocyte-specific deletion of Cox-2
COX	cyclooxygenase
cPGES	cytosolic PGE_2 synthase
CRTH2	chemoattractant receptor-homologous molecule expressed on T helper type 2 cells
CVD	cardiovascular disease
DPr	prostaglandin D receptor
EC	endothelial cell
EPr	prostaglandin E receptor
ERK1/2	extracellular signal-regulated kinase 1/2
FPr	prostaglandin F receptor
H-PGDS	hematopoietic prostaglandin D_2 synthase
HF	heart failure
HDL	high-density lipoprotein
HSD	high-salt diet
I/R	ischemia/reperfusion
IPr	prostacyclin receptor
KO	knockout
L-PGDS	lipocalin prostaglandin D_2 synthase
MI	myocardial infarction
MMP	matrix metalloprotease
mPGES	microsomal prostaglandin E_2 synthase
PG	prostaglandin
PGFS	prostaglandin F_2 synthase
PGI_2	prostacyclin
PGIS	prostacyclin synthase
PPARγ	peroxisome proliferator-activated receptor gamma
SNP	single-nucleotide polymorphism
TBXS	thromboxane synthase
TGF	transforming growth factor
TPr	thromboxane receptor
TxA2	thromboxane A2
VSMC	vascular smooth muscle cell

outline the role of prostanoids in myocardial and vascular remodeling and explore how maladaptive remodeling can be counteracted by targeting specific prostanoids.

Highlights

- Prostanoids play an important role in modulating structural and functional changes occurring in the myocardium and in the vasculature in response to physiological and pathological stimuli.
- COX (cyclooxygenase)-1–derived prostanoids have a protective effect in myocardium and vascular remodeling, while the effect of COX-2–derived prostanoids is more complicated. It depends on the cell type in which COX-2 is expressed and the substrate rediversion consequent to its deletion or inhibition.
- The use of NSAIDs, which reduce the biosynthesis of prostanoids by inhibiting COX isozymes, is associated with an increased risk of cardiovascular events, including myocardial infarction, stroke, hypertension, and heart failure.
- Targeting specific prostanoid synthases or their receptors may represent a novel effective strategy to prevent or mitigate adverse cardiovascular remodeling.

COX-1 AND COX-2 IN THE CARDIOVASCULAR SYSTEM

The COX enzyme exists as 2 isozymes, known as COX-1 and COX-2. COX-1 is constitutively expressed in most cell types and is responsible, in the main, for homeostatic functions.[1] COX-2 is usually an inducible enzyme, which is mostly expressed in the setting of inflammatory states.[1] COX-2 is also constitutively expressed in the brain, the vasculature, and the kidney. However, these distinctions between COX-1 and COX-2 are relative rather than absolute, and their expression and function are context dependent.[1,2] The COX enzymes convert AA into unstable cyclic endoperoxides, PGG_2 and PGH_2, which are then metabolized by tissue-specific isomerases and synthases into PGE_2, PGD_2, $PGF_{2\alpha}$, PGI_2, and TxA_2. Receptors for PGE_2 (EPr [PGE receptor] 1–4), PGD_2 (DPr [PGD receptor] 1–2), $PGF_{2\alpha}$ (FPr [PGF receptor]), PGI_2 (IPr [prostacyclin receptor]), and TxA_2 (TPr [thromboxane receptor]) are linked to G proteins, the expression of which is also tissue and cell specific (Figure).

Several genetic variants of *COX-1* and *COX-2* genes have been associated with cardiovascular disease (CVD). The *COX-1* C50T single-nucleotide polymorphism (SNP) reduces response to aspirin but does not modify the risk of atherothrombotic events in White people.[11,12] In a Swedish cohort, the *COX-1* SNP rs883484 TT was associated with increased formation of $PGF_{2\alpha}$, while the COX-1 SNP rs10306135 TT was associated with decreased formation of $PGF_{2\alpha}$ and lower prevalence of CVD.[13] The *COX-1* rs1330344 SNP CC genotype is associated with an increased risk of subsequent vascular

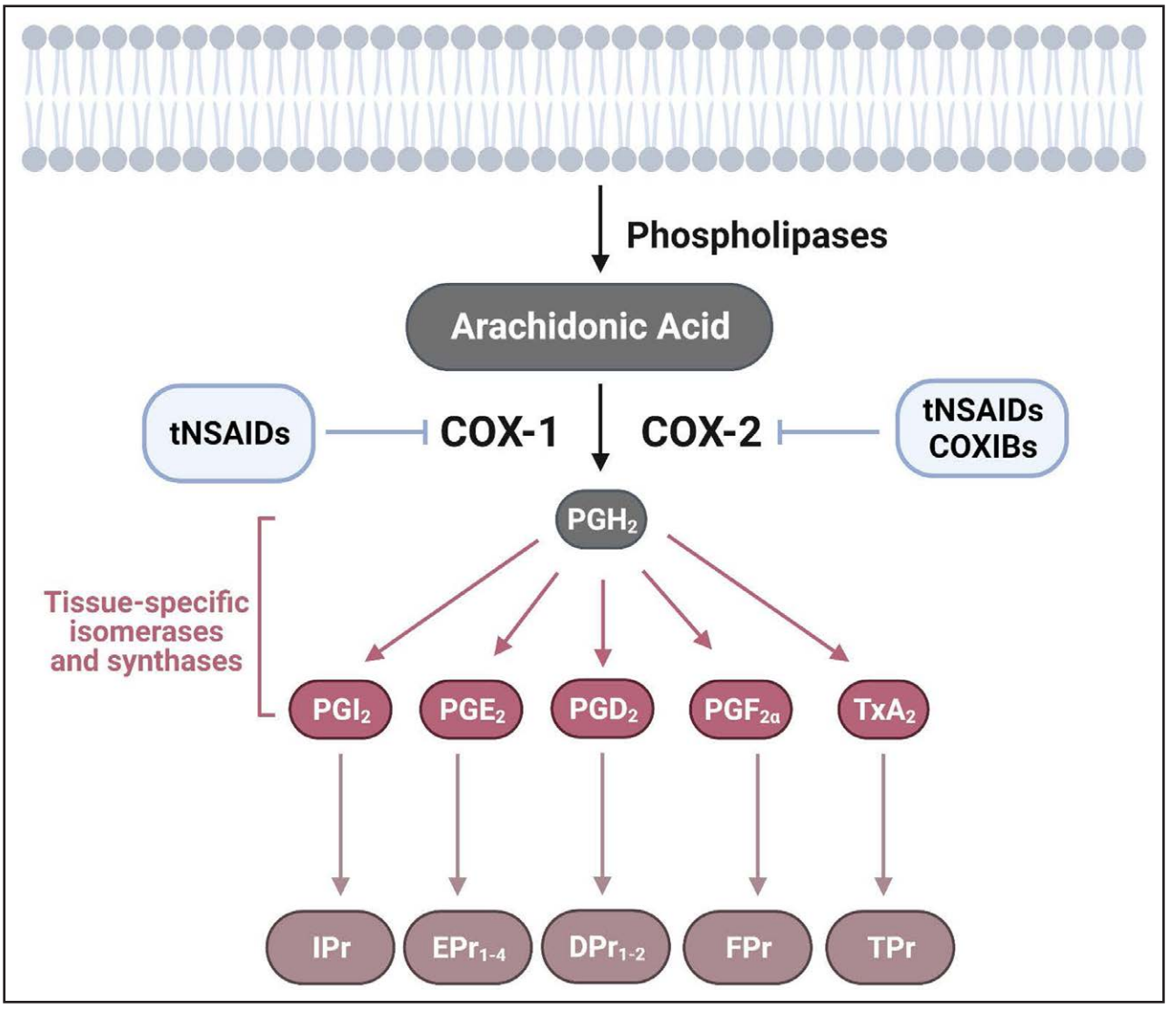

Figure. An overview of the arachidonic acid pathway.
Arachidonic acid, after it is cleaved by cellular membranes, the phospholipase A_2 enzymes, is metabolized by the COX (cyclooxygenase) enzymes (COX-1 and COX-2) to form the unstable metabolite prostaglandin (PG)H_2. Tissue-specific isomerases and synthases further metabolize PGH_2 to form the different prostanoids: prostacyclin (PGI_2), PGE_2, PGD_2, $PGF_{2\alpha}$, and thromboxane A_2 (TxA_2). Prostanoids exert their biological effects by interacting with G-protein–coupled receptors: IPr (PGI_2 receptor), EPr (PGE_2 receptor), DPr (PGD_2 receptor), FPr ($PGF_{2\alpha}$ receptor), and TPr (TxA_2 receptor). Traditional NSAIDs (tNSAIDs) inhibit the activity of both COX-1 and COX-2. Coxibs (NSAID selective for COX-2 inhibition) inhibit only the activity of COX-2. Created with BioRender.com.

events in Chinese patients with ischemic stroke treated with aspirin[14] and with an increased risk of Kawasaki disease and coronary artery injury in Chinese children.[15]

There are >50 active SNPs in human *COX-2*, but most of them are in silent sites. The *COX-2* rs20417 GC genotype reduces promoter activity[16] and COX-2 expression[14] and is associated with decreased cardiovascular risk in White people.[17,18] In contrast, the same *COX-2* SNP is associated with increased risk for MI in Chinese[19] and coronary artery disease in Koreans,[20] and it is more common in Black people with stroke.[21] In addition, 3 SNPs (rs689466, rs2066826, and rs20417) in the *COX-2* gene cosegregate with either coronary or carotid calcified plaque risk in diabetics in a White population.[22] The *COX-2* rs20417 SNP is associated with a reduced risk for major cardiovascular events and lower TxA_2 and PGI_2.[23] The *COX-2* rs5277 C allele is associated with increased risk for coronary artery disease and adverse cardiac and cerebrovascular events after coronary artery bypass grafting in Chinese.[24] The *COX-2* rs12042763 and rs689466 SNPs are associated with changes in blood pressure (BP) in response to a low-salt diet or high-salt diet (HSD) in Chinese adults.[25]

These genome-wide association studies indicate that genetic variants in COX genes may influence the risk for CVD and the type of association is affected by genetic ancestry.

COX-1 AND COX-2 IN MYOCARDIAL REMODELING

COX-1 is the main isoform expressed constitutively in the normal heart. COX-2 expression is increased in response to stressor events.[2] Myocardial COX-2 expression is higher in patients with cardiomyopathies compared with healthy subjects.[26] In the rat heart, Cox-2 expression increases significantly with age, whereas Cox-1 expression remains unchanged, indicating a role for COX-2 in myocardial age-related remodeling.[27]

Genetic disruption or pharmacological inhibition of COX-1 in mice increases cardiac ischemia/reperfusion (I/R) injury, due to reduction of the cardioprotective PGI_2 and PGE_2.[28] In contrast, Cox-1 and Pgis (PGI_2 synthase) overexpression confers protection against ischemic stroke and cardiovascular damage and prolongs life span.[29]

In mice, conditioned by genetic background, prenatal genetic disruption of Cox-2 reduces the survival rate due to cardiorenal anomalies attributable to the absence of Cox-2 during development. Surviving Cox-2 knockout (KO) mice present myocardial fibrosis[30] and an exacerbation of reperfusion injury.[28] Adult Cox-2–deficient rats, but not Cox-1–deficient rats, exhibit myocardial fibrosis, a reduction of cardiac ATP and acetyl-CoA production, increased mortality, and comparatively preserved ejection fraction. Thus, while ejection fraction is reduced compared with wild-type rats, it is still above 50%.[31] Similarly, CM-Cox-2 KO (cardiomyocyte-specific deletion of Cox-2) mice exhibit perivascular and interstitial myocardial fibrosis, hypertrophy, arrhythmia, and reduced exercise tolerance, while ejection fraction is preserved.[32] Since BP is similar in wild-type and CM-Cox-2 KO mice, these data are consistent with a direct role of COX-2 in myocardial remodeling.[32] In contrast, Cox-2 overexpression in cardiomyocytes confers cardioprotection against I/R injury perhaps due to increased PGE_2 both in ex vivo[33] and in vivo[34] models. However, these transgenic mice develop cardiac hypertrophy and activation of a fetal gene program, although cardiac function remains normal.[35]

Mixed results arise from animal studies investigating the effect of NSAIDs in cardiac remodeling.[2] Consistent with the phenotype observed in rodents lacking Cox-2, mice treated with diclofenac present with impairment of diastolic but not systolic function, reduced calcium transients, and cardiac mitochondrial dysfunction.[36] DFU—a selective COX-2 inhibitor—reduces infarct size and improves ventricular performance in infarcted rats.[37] NS-398 and rofecoxib—2 selective COX-2 inhibitors—do not affect infarct size, but they reduce cardiac hypertrophy and collagen deposition in murine hearts post-MI.[38] Celecoxib protects against abdominal aortic constriction–induced cardiac hypertrophy in rats.[39] Aspirin does not have an effect on cardiac remodeling and function after MI but reduces the expression of proinflammatory cytokines in the infarcted heart.[40] Deleterious cardiac effects are reported with celecoxib and NS-398 in the late phase of ischemic preconditioning in rabbits,[41] with celecoxib after MI in pigs[42] and with rofecoxib after MI in hyperlipidemic mice.[43] These conflicting results may result from differences in experimental design (disease model, drug regimen, species, sex, and genetic background).

In summary, COX-1 has a protective effect in myocardial remodeling, while the role of COX-2 is more controversial (Table 1).

COX-1 AND COX-2 IN VASCULAR REMODELING

In the vasculature, COX-1 and COX-2 are expressed in both vascular smooth muscle cells (VSMCs) and endothelial cells (ECs), and the extent of this expression is modulated by pathophysiological conditions.[2] Human atherosclerotic vessels exhibit increased expression of both COXs, with COX-2 localized mainly in proliferating VSMCs, and macrophages.[44] High COX-2 and MMP (matrix metalloproteinase)-9 expression in macrophages in human atherosclerotic plaques is associated with an increased risk of cerebrovascular symptoms.[45] In mice, Cox-1 genetic deletion or pharmacological inhibition retards the development of atherosclerotic lesions[46–48] and prevents the increase in BP in response to Ang II (angiotensin II) infusion.[49] In contrast, Cox-1 deletion in bone marrow cells accelerates the development of early atherosclerotic plaques in hyperlipidemic mice.[50] Endothelial-specific Cox-1 deletion retards atherosclerosis and reduces vascular inflammation and the contractile response to vascular pressors.[51] Consistently, Cox-1 deletion or inhibition reduces endothelial-dependent contraction both in atherosclerotic and nonatherosclerotic arteries.[52]

Although the use of NSAIDs increases the risk for cardiovascular events in humans,[7] Cox-2 deletion or inhibition accelerates, leaves unaltered, or retards lesion progression in mice.[53–61] Global postnatal deletion of Cox-2, generated to overcome the multiple abnormalities observed in the conventional Cox-2 KOs, and vascular Cox-2 deletion result in accelerated atherogenesis.[62,63] The deletion of Cox-2 in myeloid cells retards atherogenesis while its deletion in $CD4^+$ T cells has no detectable effect on lesion burden.[64] However, T-regulatory cells may stabilize atherosclerotic plaques by reducing the expression of COX-2 in vulnerable plaque and particularly in macrophages.[65]

COX-2–derived prostanoids contribute to BP control by regulating vascular tone and renal sodium transport. Both traditional NSAIDs and coxibs may increase BP in normotensive individuals and in patients with hypertension.[66,67]

Table 1. In Vivo Preclinical Studies Assessing the Effect of COXs in Cardiac Remodeling

Species	Intervention	Preclinical model	Phenotype	Mechanism	References
Mouse	Cox-1 deletion Indomethacin Cox-2 deletion	Cardiac I/R	↓Cardiac function		28
Mouse	Cox-1 and PGIS overexpression	Chemical-induced thrombosis AA-induced thrombotic heart arrest Ang II–induced peripheral reperfusion damage	↓Acute thrombotic stroke ↓Arterial arrest ↓Vasoconstrictive damage ↑Life span		29
Mouse	Cox-2 deletion		↑Cardiac fibrosis ↓Survival		30
Rat	Cox-1 deletion		None	↓Cardiac energy metabolism	31
	Cox-2 deletion		↓Cardiac function ↑Cardiac fibrosis ↓Survival		
Mouse	Cardiomyocyte Cox-2 deletion		↓Exercise tolerance ↑Cardiac hypertrophy ↑Cardiac fibrosis Arrhythmia		32
Mouse	Cardiac Cox-2 overexpression	Cardiac I/R	↓Infarct size	↑PGE_2	34
Mouse	Cardiac Cox-2 overexpression		↑Cardiac hypertrophy	↑PGE_2	35
Mouse	Diclofenac		Diastolic dysfunction ↑Cardiac fibrosis	↑Mitochondrial oxidative stress ↑Proinflammatory cytokines	36
Mouse	Cox-2 inhibitor (DFU)	MI	↓Infarcted size ↓LV pressure Improved contractility		37
	Aspirin	MI	None		
Mouse	Cox-2 inhibitor (NS-398) Rofecoxib	MI	↑Cardiac function ↓Cardiac hypertrophy ↓Cardiac fibrosis	↓TGF-β	38
Rat	Celecoxib	Abdominal aortic constrictions	↑Cardiac function ↓Cardiac hypertrophy ↓Cardiac fibrosis	↓Inflammation (AKT/mTOR/NF-κB) ↓Apoptosis (MDM2-p53) ↓Oxidative stress (NRF-2)	39
Mouse	Aspirin	MI	None	↓TNFα ↓IL-1β	40
Rabbit	Cox-2 inhibitor (NS-398) Celecoxib	Late phase of ischemic preconditioning	↑Myocardial stunning ↑Infarct size		41
Pig	Celecoxib	MI	↓Cardiac function ↑Cardiac hypertrophy ↑Cardiac fibrosis ↑Mortality	↓Collagen fiber density	42
Mice	Rofecoxib	Hyperlipidemia (APOE*3Leiden mice) I/R	↓Cardiac function		43

AA indicates arachidonic acid; AKT, protein kinase B; Ang II, angiotensin II; Cox, cyclooxygenase; I/R, ischemia/reperfusion; IL, interleukin; LV, left ventricle; MDM2, mouse double minute 2 homolog; MI, myocardial infarction; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa B; NRF-2, nuclear factor erythroid 2-related factor 2; PGE_2, prostaglandin E_2; PGIS, prostacyclin synthase; TGF-β, transforming growth factor-beta; and TNF-α, tumor necrosis factor-alpha.

Although postnatal Cox-2 KO mice have normal BP,[62] Cox-2 deletion or inhibition exaggerates hypertension after Ang II infusion[48] or in response to low-salt diet or HSD.[68] Mice in which Cox-1 is placed under the Cox-2 promoter are hypertensive.[69] Vascular Cox-2 KO mice challenged with HSD also exhibit hypertension.[70] The hypertensive phenotype consequent to Cox-2 deletion is consistent with the suppression of vasorelaxant PGI_2 and PGE_2.

Overall, COX-1 has a protective effect in vascular remodeling. The effect of COX-2 depends on the cell type in which it is expressed and the substrate rediversion consequent to its deletion or inhibition (Table 2).

Table 2. In Vivo Preclinical Studies Assessing the Effect of COXs in Vascular Remodeling

Species	Intervention	Preclinical model	Phenotype	Mechanism	References
Mouse	Cox-1 deletion	Atherosclerosis (ApoE KO) Carotid ligation	↓Athero plaque formation ↓Platelet-vessel wall interactions	↓TxBM ↓PGIM	46
Mouse	Cox-1 inhibitor (SC-560) TPr antagonist (BM-573)	Atherosclerosis (Ldlr KO)	↓Athero plaque formation ↑Plaque stability	↓TxBM ↓Vascular inflammation (CD40L)	47
Mouse	Cox-1 inhibitor (SC-560)	Atherosclerosis (ApoE KO)	↓Athero plaque formation	↓TxBM ↓Vascular inflammation (CD40L) ↓Apoptosis (Bax)	48
Mouse	Cox-1 deletion Cox-1 inhibitor (SC-58560)	Ang II infusion	↓Hypotension	↑Medullary PGI_2 and PGE_2	49
	Cox-2 deletion Cox-2 inhibitor (SC58236)	Ang II infusion	↑Hypertension		
Mouse	Bone marrow Cox-1 deletion	Atherosclerosis (ApoE KO or Ldlr KO)	↑Athero plaque formation	↑Cox-2 expression in macrophages	50
Mouse	Bone marrow Cox-1 deletion	Atherosclerosis (ApoE KO)	↓Athero plaque formation	↓Inflammation (IL-6, VCAM, P-selectin)	51
Mouse	Cox-1 deletion	Atherosclerosis (ApoE KO)	↓Athero plaque formation		52
Mouse	Cox-2 inhibitor (MF-tricyclic)	Atherosclerosis (ApoE KO)	↑Athero plaque formation		53
Mouse	Cox-2 inhibitor (MF-tricyclic) Sulindac	Atherosclerosis (ApoE KO)	No effect on athero plaque formation		54
Mouse	Nimesulide Indomethacin	Atherosclerosis (Ldlr KO)	No effect on athero plaque formation ↓Athero plaque formation	↓PGIM ↓Inflammation (sICAM-1, MCP-1) ↓PGIM ↓TxBM	55
Mouse	Celecoxib	Atherosclerosis (ApoE KO)	No effect on advanced athero plaque formation		56
Mouse	Rofecoxib Indomethacin Hematopoietic Cox-2 deletion	Atherosclerosis (Ldlr KO)	↓Athero plaque formation		57
Mouse	Rofecoxib Cox-2 inhibitor (NS-398) Indomethacin Hematopoietic Cox-2 deletion	Atherosclerosis (ApoE KO)	↓Athero plaque formation		58
Mouse	Celecoxib	Atherosclerosis (ApoE KO)	↓Athero plaque formation	↓Inflammation (ICAM-1, VCAM-1)	59
Mouse	Celecoxib Rofecoxib Naproxen	Atherosclerosis (ApoE KO)	No effect on initiation and progression of atherosclerosis		60
Mouse	Parecoxib	Atherosclerosis (ApoE KO)	↑Athero plaque stability	↓Inflammation (VSMCs, macrophages, collagen, MMPs)	61
Mouse	Postnatal Cox-2 deletion	Atherosclerosis (ApoE KO)	↑Athero plaque formation Normal BP	↑Inflammation (VSMCs, leukocytes)	62
Mouse	EC Cox-2 deletion VSMC Cox-2 deletion EC/VSMC Cox-2 deletion	Atherosclerosis (Ldlr KO)	↑Athero plaque formation	↑Inflammation ↑TxBM ↑Cox-2 expression in macrophages	63
Mouse	Macrophage Cox-2 deletion	Atherosclerosis (Ldlr KO)	↓Athero plaque formation	↓Inflammation ↑Cox-2 expression in VSMCs	64
	T-cell (CD4+) Cox-2 deletion		No effect on atherogenesis		
Mouse	Cox-2 deletion	LSD HSD	↑Hypertension ↑Hypertension		68

(*Continued*)

Table 2. Continued

Species	Intervention	Preclinical model	Phenotype	Mechanism	References
Mouse	COX-1>COX-2	HSD	↑Hypertension	↓PGI_2 in renal medulla	69
Mouse	EC/VSMC Cox-2 deletion	HSD	↑Hypertension	↓PGIM ↓NO	70

Ang II indicates angiotensin II; Athero, atherosclerosis; Bax, Bcl-2 associated X-protein; BP, blood pressure; Cox, cyclooxygenase; EC, endothelial cell; HSD, high-salt diet; ICAM-1, intracellular adhesion molecule-1; IL-6, interleukin-6; Ldlr, low-density lipoprotein receptor; LSD, low-salt diet; MMP, metalloproteinase; MCP-1, monocyte chemoattractant protein-1; PGE_2, prostaglandin E2; PGI_2, prostacyclin; PGIM, urinary prostacyclin metabolite; sICAM, soluble intercellular adhesion molecule; TxBM, urinary thromboxane metabolite; VCAM, vascular cell adhesion molecule; and VSMC, vascular smooth muscle cell.

PGI_2 IN THE CARDIOVASCULAR SYSTEM

PGI_2, synthesized mainly by COX-2 and the downstream enzyme PGIS, exerts its actions through the IPr, which is expressed in many different tissues/cells including the heart and vasculature.[3,71] IPr can function as a homodimer or as a heterodimer with TPr.[3]

In humans, common variants in the *PTGIS* gene are associated with MI risk.[72] The *PTGIS* rs5629 SNP is associated with MI in a Japanese population[73] and with carotid artery or intracranial arterial stenosis in a Chinese population,[74] while the *PTGIS* 1117C→A SNP is associated with hypertension.[75]

The R212C SNP in the gene encoding for IPr, *PTGIR*, which blunts PGI_2 signaling, leads to accelerated atherothrombosis, and it is associated with intimal hyperplasia of the common carotid arteries.[76,77] The *PTGIR* V53V/S328S SNPs are associated with platelet activation in patients with deep vein thrombosis.[77]

Altogether, these genomic studies consistently indicate a cardioprotective role of the PGI_2 signaling pathway.

PGI_2 IN MYOCARDIAL REMODELING

Mice lacking IPr develop salt-sensitive hypertension, cardiac hypertrophy, and fibrosis.[78] Increased cardiac fibrosis is also observed in hypercholesterolemic IPr KO mice infused with Ang II.[79] Moreover, IPr KO mice present an increased hypertrophic response to aortic banding[80] and infarct size following I/R,[81] while myocardial tension and coronary flow rate are reduced.[81] In contrast, beraprost—a PGI_2 analogue—reduces myocardial fibrosis and hypertrophy in salt-sensitive hypertensive rats treated with HSD.[82] Similarly, ONO-1301—a synthetic PGI_2 agonist—reduces cardiac fibrosis, left ventricular dilation, and systolic dysfunction in response to pressure overload.[83] The antifibrotic effect of PGI_2 may be mediated via the TGF (transforming growth factor)-β1 signaling pathway.[83–85] PGI_2 analogs increase myocardial contractility in the absence of changes in heart rate or BP, while leaving active relaxation and diastolic function intact in pigs.[86,87]

Inhaled iloprost—an analogue of PGI_2—improves myocardial performance and right ventricular systolic function during exercise by increasing LV global longitudinal strain reserve and decreasing LV diastolic filling load and pulmonary hypertension[88] in patients with HF with preserved ejection fraction.

In summary, these studies provide evidence for a direct protective role of PGI_2 against maladaptive myocardial remodeling and indicate that PGI_2 analogs may be beneficial for the treatment of patients with HF with preserved ejection fraction (Table 3).

PGI_2 IN VASCULAR REMODELING

PGI_2 is produced at low levels by the vasculature of healthy subjects, but its levels are significantly increased as a constraint on accelerated platelet vascular interactions in patients with atherosclerosis.[44,89]

IPr deletion accelerates atherosclerosis in hyperlipidemic mice.[90] The atherosclerotic plaques of IPr KO mice present partial endothelial disruption and increased platelet activation and leukocyte-EC interactions.[90] Moreover, IPr KO mice exhibit increased luminal stenosis following carotid vascular injury due to neointimal proliferation.[91] Likewise, IPr deletion or COX-2 inhibition increases vascular hyperplasia in response to hemodynamic stress.[92] In contrast, gene transfer of human PGIS into endothelium-denuded carotid arteries of rats increases PGI_2 production and reduces the neointima-media ratio.[93] Similarly, a PGI_2 analogue reduces intimal thickness in arterial anastomoses in hyperlipidemic rabbits.[94]

In the presence of a dysfunctional IPr or high concentrations of an IPr agonist, PGI_2 can also bind TPr_α, but not TPr_β, in human VSMCs, causing its inhibition.[95] Iloprost promotes VSMC proliferation and switching to a synthetic phenotype in human cells lacking the IPr. These effects are prevented by the TPr antagonist S18886 or TPr knockdown, indicating a dependence on the TPr.[96] In vivo studies are necessary to confirm the functional effect of PGI_2 on TPr.

PGI_2 also plays an important role in controlling vascular homeostasis. Basal BP is similar in IPr KO mice and their wild-type controls.[80,97] In response to HSD, IPr KO mice may present increased or reduced BP, depending on the experimental conditions.[78,98–100] Iloprost mediates endothelium-dependent relaxations in the mouse vasculature via the activation of cGMP and cAMP pathways.[101] Beraprost prevents vascular stiffness in elderly with cerebral infarction.[102]

Overall, PGI_2 plays a beneficial effect against maladaptive vascular remodeling (Table 4).

Table 3. In Vivo Preclinical Studies Assessing the Effect of Prostacyclin in Cardiac Remodeling

Species	Intervention	Preclinical model	Phenotype	Mechanism	References
Mouse	IPr deletion	Normal diet LSD HSD	↑Hypertension ↑Cardiac hypertrophy ↑Cardiac fibrosis		78
	IPr/TPr deletion	Normal chow diet	↑Hypertension		
Mouse	IPr deletion	Hypercholesterolemia (ApoE KO) Ang II	↑Cardiac fibrosis	↓cAMP ↓CREB phosphorylation	79
Mouse	IPr deletion	Pressure overload (TAC)	Normotensive ↑Cardiac hypertrophy ↑Cardiac fibrosis		80
Mouse	IPr deletion	I/R	↑Infarcted area		81
	TPr deletion		None		
Salt-sensitive Dahl rat	PGI_2 analog (Beraprost)	HSD	↑Diastolic function ↓Cardiac hypertrophy ↓Cardiac fibrosis ↑Survival		82
Mouse	PGI_2 analog (ONO-1301)	Pressure overload (TAC)	↑Systolic function ↓Cardiac hypertrophy ↓Cardiac fibrosis	↓TGF-β–induced fibroblast-to-myofibroblast transition	83
Pig	PGI_2 analogs (Epoprostenol, Iloprost)		↑LV contractility		86
Pig	PGI_2 analogs (Epoprostenol, Iloprost)		Preservation of EDP		87

Ang II indicates angiotensin II; CREB, cAMP response element binding; EDP, end diastolic pressure; HSD, high-salt diet; I/R, ischemia/reperfusion; IPr, prostacyclin receptor; KO, knockout; LSD, low-salt diet; LV, left ventricle; PGI_2, prostacyclin; TAC, transverse aortic constriction; TGF-β, transforming growth factor-beta; and TPr, thromboxane A_2 receptor.

TXA_2 IN THE CARDIOVASCULAR SYSTEM

TxA_2 is highly unstable, rapidly hydrolyzed to the biologically inactive, more stable marker thromboxane B_2 itself subject to further metabolism. TxA_2 is produced mainly by platelet COX-1 and the downstream enzyme TBXS (thromboxane synthase) and exerts its biological functions via TPr, which exists in 2 spliced isoforms in humans, TPr_α (the only isoform expressed in mice) and TPr_β. TPr can associate to form homodimers and heterodimers. In addition, TPr_a can heterodimerize with IPr, which promotes a cAMP generation like IPr activation and relocation in lipid rafts.[3] Other lipid mediators, like PGI_2, isoprostanes, and hydroxyeicosatetraenoic acids, can activate the TPr at high concentrations in vitro and in vivo.[95,103,104] Moreover, the inhibition of TBXS determines PGH_2 accumulation, which can also activate TPr. Therefore, although the biological significance of TPr activation by different ligands is not completely understood, this may limit the therapeutic efficacy of TBXS inhibitors. Indeed, the TBXS inhibitor dazmegrel failed to advance in clinical development for the treatment of CVD.[105]

There are genetic variants for *TBXAS1*, the gene encoding for TBXS, and *TBXA2R*, the gene encoding for TPr. Common SNPs in the *TBXAS1* gene are associated with MI risk,[72] while the rs41708 SNP is associated with symptomatic carotid artery disease or intracranial arterial stenosis.[74,106] Several TPr variants are associated with changes in platelet function and CVD: the variant V80E is associated with inhibition of platelet activation, the variant rs1TXB131882 is associated with carotid plaque vulnerability,[106] the variant A160T is associated with platelet activation,[107] and the variant rs13306046 is associated with BP reduction.[108]

Collectively, genome-wide association studies reveal the importance of the TxA_2 signaling pathway in the cardiovascular system.

TXA_2 IN MYOCARDIAL REMODELING

TPr deletion, TXBS inhibition, or TPr antagonism limits infarct size in rodents after I/R in vivo.[109–111] Moreover, TPr deletion ameliorates cardiac hypertrophy and fibrosis caused by IPr deletion[78] and reduces lipopolysaccharide-induced tachycardia.[112] TPr antagonism reduces the pressor response to electrically induced muscle contraction in rats with HF[113] and protects from right ventricular pressure overload.[114,115] In contrast, a TPr agonist evokes ventricular arrhythmia in anesthetized rabbits.[116]

In patients with HF, urine thromboxane B_2 metabolite levels are independently associated with the risk of death and the need for transplant or mechanical support.[117]

Altogether, TxA_2 contributes to CVD by favoring adverse cardiac remodeling, in addition to inducing platelet aggregation (Table 5).

TXA_2 IN VASCULAR REMODELING

COX-1–dependent TxA_2 formation is increased in subjects with severe atherosclerosis reflecting accelerated

Table 4. In Vivo Preclinical Studies Assessing the Effect of Prostacyclin in Vascular Remodeling

Species	Intervention	Preclinical model	Phenotype	Mechanism	References.
Mouse	IPr deletion	Atherosclerosis (ApoE KO)	↑Athero plaque formation	↑ICAM-1 ↓PECAM-1	90
	TPr deletion		↓Athero plaque formation		
Mouse	IPr deletion	Vascular injury	↑Vascular proliferation and platelet activation		91
	TPr deletion TPr antagonist (S18886)		↓Vascular proliferation and platelet activation		
Mouse	IPr deletion	Transplant arteriosclerosis Common carotid artery ligation	↑Neointimal hyperplasia	↑TxA_2 ↑8, 12-iso-$iPF_{2\alpha}$-VI	92
	Nimesulide		↓Blood flow		
	TPr deletion+ nimesulide		No effect		
Rat	PGIS overexpression	Vascular injury (carotid balloon injury)	↓Neointimal hyperplasia	↑PGI_2	93
Rabbit	PGI_2 analogue (TRK-100)	Hypercholesterolemia (diet+1% cholesterol) Reanastomosis of abdominal aorta	↓Intimal proliferation	↑PGI_2 ↓TxA_2	94
Mouse	IPr deletion	Regular chow diet	Normotensive Normal heart rate		97
Mouse	IPr deletion	Regular chow diet HSD	Hypotension Hypertension Normotensive		98
	TPr deletion	Regular chow diet HSD	Normotensive		
Mouse	IPr deletion	HSD	Hypertension Cardiac fibrosis		99
Mouse	IPr deletion	Hypercholesterolemia (Ldlr KO) HSD	Hypotension (male mice) Normotensive (female mice)		100

Athero indicates atherosclerosis; HSD, high-salt diet; ICAM, intracellular adhesion molecule; iPF, isoprostane F; IPr, prostacyclin receptor; KO, knockout; Ldlr, low-density lipoprotein receptor; PECAM-1, platelet endothelial cell adhesion molecule-1; PGI_2, prostacyclin; TPr, thromboxane A_2 receptor; and TxA_2, thromboxane A_2.

platelet-endothelium interactions.[44,89,118] Consistently, the deletion or blockade of TPr delays atherogenesis in hyperlipidemic or diabetic mice.[90,119–121] Moreover, TPr antagonism or TBXS inhibition decreases atherogenesis, delays progression of established atherosclerotic lesions, decreases BP, and improves vascular dysfunction in hyperlipidemic mice.[122–124] The role of TxA_2 in atherosclerosis is mediated by the expression of TPr in VSMCs but not in ECs or bone marrow cells.[125,126]

Genetic deletion or pharmacological blockade of the TPr attenuates the response to vascular injury in mice.[91] TPr KO mice exhibit reduced neointimal hyperplasia in response to COX-2 inhibition or carotid ligation.[92] Furthermore, Tbxs and TPr KO mice have a reduced infarct size after I/R and chemical-induced vascular injury due to reduced oxidative damage.[110] Inhibition of TBXS or the TPr blockade does not affect baseline BP. However, TPr KO mice have a reduced hypertensive response to Ang II and L-NAME, suggesting an interaction between the TxA_2 and Ang II/NO vasoresponsive pathways.[127–129] Deletion of TPr in VSMCs reduces hypertension and aortic remodeling in response to Ang II but not in unchallenged mice.[130] Moreover, a TPr antagonist prevents the development of aortic hyperplasia and vascular fibrosis in spontaneously hypertensive stroke-prone rats.[131]

In summary, the Tbxs-TxA_2-TPr pathway has a deleterious effect in vascular remodeling (Table 6). In contrast to TBXS inhibition, TPr blockade could represent a good therapeutic target for the treatment of atherosclerosis progression, vascular injury, and hypertension. Clearly, the competition is low-dose aspirin, and an advantage depends, at least to some extent, on the theoretical activation of TPr by noncanonical ligands, like the isoprostanes, without any impact on the biosynthesis of PGI_2. Currently, the TPr antagonist ifetroban is under clinical development for several therapeutic indications, including CVD (https://www.clinicaltrials.gov; unique identifier: NCT03962855).

PGE_2 IN THE CARDIOVASCULAR SYSTEM

PGE_2 is formed from PGH_2 by the action of 3 different synthases: mPGES (microsomal PGE_2 synthase)-1, mPGES-2, and cPGES (cytosolic PGE_2 synthase).[3]

PGE_2 is synthetized in many different cell types, and, like PGD_2 and $PGF_{2\alpha}$, it is inactivated by 15-hydroxyprostaglandin dehydrogenase, resulting in 15-keto-PGE_2.[3] PGE_2 exerts its biological function via binding to 4 EPrs, which activate different cellular signaling pathways.

Table 5. In Vivo Preclinical Studies Assessing the Effect of Thromboxane A_2 in Cardiac Remodeling

Species	Intervention	Preclinical model	Phenotype	Mechanism	References
Rat	TBXS inhibitor (U-63,557A) TPr antagonist (SQ-29,548)	I/R	↓Infarct size	↓Neutrophil infiltration	109
Mouse	TXBS deletion TPr deletion	I/R	↓Infarct size	Restoration microcirculation	110
Rat	IPr agonist/TXBS inhibitor (ONO-1301)	I/R	↓Infarct size ↓Cardiac fibrosis	↑Hepatocyte growth factor	111
Mouse	TPr deletion FPr deletion	LPS	↓Tachycardia		112
Rat	TPr antagonist (daltroban)	MI	↓Exercise pressor reflex		113
Mouse	TPr antagonist (CPI211)	Pressure overload (pulmonary artery banding)	↓Cardiac fibrosis ↓Cardiac hypertrophy	↓TGF-β signaling.	114
Mouse	TPr antagonist (NTP42)	Pulmonary hypertension (monocrotaline) Pressure overload (pulmonary artery banding)	↓Cardiac fibrosis ↓Cardiac hypertrophy		115
Rabbit	TPr agonist (U-46619)		Arrhythmia		116

I/R indicates ischemia/reperfusion; IPr, prostacyclin receptor; LPS, lipopolysaccharide; MI, myocardial infarction; TGF-β, transforming growth factor-beta; TPr, thromboxane A2 receptor; and TXBS, thromboxane A_2 synthase.

Only genetic variants for *PTGER2*—the gene encoding for EPr2—have a recognized association with with CVD. The *PTGER2* 2-1-1 haplotype is associated with reduced risk of MI and the 2-2-1 haplotype, with reduced risk of ischemic stroke.[132] Moreover, the *PTGER2* rs17197 SNP AA genotype is more frequent in subjects with essential hypertension in men,[133] and the *PTGER2* rs70s8494 SNP GG genotype is less common in subjects with acute coronary syndromes than in those with stable coronary disease.[134]

The current genome-wide association studies provide only a partial understanding of the complex role played by PGE_2 signaling in the cardiovascular system.

PGE_2 IN MYOCARDIAL REMODELING

There are conflicting data on the role of PGE_2 in I/R and MI resulting from different experimental conditions. Global mPGES-1 deletion exacerbates I/R injury due to the impairment of cardiac microcirculation and increased inflammation.[135] Global or bone marrow–derived myeloid cell mPGES-1 deletion impairs cardiac function and induces cardiac hypertrophy in infarcted mice[136]; however, only the deletion of the enzyme in myeloid cells increases mortality.[137] In both genetic models, COX-dependent inflammatory cell infiltration in the myocardium contributes to the maladaptive remodeling consequent to mPGES-1 deletion. In contrast, mPGES-1 deletion in myeloid cells improves the post-MI survival rate without affecting cardiac function, fibrosis, hypertrophy, and infarct size.[138] mPGES-1 inhibition, but not celecoxib, improves cardiac fibrosis and reduces infarct size after MI,[139] due to the shunting of PGH_2 to the cardioprotective PGI_2.[139,140]

The effect of PGE_2 in adult myocardium is mediated mainly by EPr2, EPr3, or EPr4.[3]

EPr2 deletion exacerbates myocardial injury after MI by reducing inflammatory macrophages in the infarcted heart and thereby impairing cardiac repair.[141]

EPr3 deletion in macrophages retards the healing process after MI by reducing neovascularization in peri-infarct zones.[142] EPr3 overexpression in cardiomyocytes reduces fibrosis and inflammatory cell infiltration in the infarcted heart, without affecting the infarct size and cardiac hypertrophy.[143] In contrast, EPr3 overexpression globally or in cardiomyocytes reduces cardiac function and increases cardiac hypertrophy and fibrosis after I/R.[143,144] EPr3 agonists protect against I/R injury in several animal models.[145,146]

Global and endothelial-specific EPr4 deletion exacerbate infarct size after I/R[135,147] and in the late phase of ischemic preconditioning.[148] Consistently, EPr4 agonists reduce infarct size after I/R.[147,149] EPr4 deletion in cardiomyocytes or EPr4 overexpression reduces cardiac hypertrophy and fibrosis after MI,[150,151] but the former worsens cardiac function[150] while the latter improves systolic function post-infarction.[151]

In nonischemic animal models, the role of PGE_2 in cardiac remodeling varies, depending on the type of insult. Exogenous PGE_2 alleviates isoproterenol-induced cardiac failure, hypertrophy, and fibrosis via inhibition of TGF-β1–GRK2 (G-protein–coupled receptor kinase 2) interaction.[152] mPGES-1 deletion worsens LV function and hypertrophy in response to Ang II.[153] In contrast, mPGES-1 deletion prevents myocardial fibrosis in mice treated with isoproterenol and reduces cardiac hypertrophy[154] and fibrosis in mice on high-fat diet.[155] EPr3 KO and EPr4 KO mice fed on high-fat diet reveal maladaptive remodeling, characterized by hypertrophy and fibrosis.[156,157] Aged EPr4 KO male mice develop increased interstitial fibrosis, reduced LV function, and dilated cardiomyopathy compared with sex- and age-matched control mice.[158] An EPr4 agonist reduces myocardial fibrosis in response

Table 6. In Vivo Preclinical Studies Assessing the Effect of Thromboxane A_2 in Vascular Remodeling

Species	Intervention	Preclinical model	Phenotype	Mechanism	References
Mouse	TPr antagonist (nstpbp5185)	Atherosclerosis (ApoE KO)	↓Athero plaque formation	Anti-inflammatory (↓IL-6, ↓TNF-a) Antioxidative activity (↑PON-1 activity) Antiplatelet activity (↓TxA_2)	119
Mouse	TPr antagonist (S18886)	Atherosclerosis (Apobec-1/Ldlr KO)	↓Athero plaque formation No effect on athero regression		120
Mouse	TPr antagonist (S18886)	Diabetes and atherosclerosis (ApoE KO+streptozotocin)	↓Athero plaque formation	↓Endothelial dysfunction (↑eNOS, ↓ICAM-1, ↓nitrotyrosine, ↓AGEs)	121
Mouse	TXBS inhibitor/TPr antagonist (BM-573)	Atherosclerosis (Ldlr KO)	↓Athero plaque formation ↓Athero plaque progression		122
Mouse	TXBS inhibitor/TPr antagonist (BM-573)	Atherosclerosis (ApoE KO)	↓Athero plaque formation	↓ICAM-1 ↓VCAM-1	123
	Aspirin		No effect		
Mouse	TXBS inhibitor/TPr antagonist (BM-573)	Atherosclerosis (ApoE KO)	↑Endothelial relaxation ↓BP	↑NO bioavailability ↓Oxidative stress	124
Mouse	EC TPr deletion	Atherosclerosis (Ldlr KO)	No effect		125
	VSMC TPr deletion		↓Athero plaque formation		
	8-iso-$PGF_{2\alpha}$		↓Athero plaque formation		
Mouse	Bone marrow TPr KOs into WTs	Atherosclerosis (ApoE KO)	No effect		126
	Bone marrow TPr KOs into TPr KOs		↓Athero plaque formation		
Mouse	Txbs deletion TPr deletion Txbs TPr deletion Aspirin	Vascular injury I/R	↑Microvascular function ↓Infarct size	↓Oxidative damage (↑NO, ↓IL-1β, ↓apoptosis)	110
Mouse	TPr deletion	Hypertension (L-NAME+HSD)	↓BP ↓Cardiac hypertrophy ↑Kidney hypertrophy		127
Mouse	TPr deletion Cox-1 deletion	Hypertension (Ang II)	↓BP ↓Cardiac hypertrophy (C57BL/6)		128
Mouse	TPr agonist (U-46619)	Vascular hyporesponsiveness (LPS)	↑Vascular tone	↓iNOS-NO	129
Mouse	VSMC TPr deletion	Hypertension (Ang II)	↓BP ↓Vascular remodeling		130
Rat	TPr antagonist (terutroban)	Hypertension (spontaneously hypertensive stroke-prone rats+HSD)	↓Aortic hyperplasia ↓Aortic fibrosis	↓TGF-β ↓Heat shock protein-47	131

AGE indicates advanced glycation end products; Ang II, angiotensin II; Apobec, apoB mRNA editing catalytic polypeptide like; Athero, atherosclerosis; BP, blood pressure; Cox, cyclooxygenase; EC, endothelial cell; eNOS, endothelial NO synthase; HSD, high-salt diet; I/R, ischemia/reperfusion; ICAM, intracellular adhesion molecule; IL, interleukin; iNOS, inducible NO synthase; L-NAME, N (ω)-nitro-L-arginine methyl ester; Ldlr, low-density lipoprotein receptor; LPS, lipopolysaccharide; PON-1, paraoxonase-1; TGF-β, transforming growth factor-beta; TNF-α, tumor necrosis factor-alpha; TPr, thromboxane receptor; TxA_2, thromboxane A_2; TXBS, thromboxane A_2 synthase; VCAM, vascular cell adhesion molecule; VSMC, vascular smooth muscle cell; and WT, wild type.

to pressure overload[159] and reduces myocardial fibrosis, hypertrophy, and inflammation after myocarditis.[160,161]

PGE_2 also regulates cardiac contractility: it reduces cardiac contractility via the EPr3 receptor[162] and increases it via the EPr4 receptor.[162]

PGE_2 may also play a role in cardiac regeneration. PGE_2 regulates stem cell activity directly through EPr2 or indirectly by impacting the microenvironment.[163]

In summary, these studies establish that PGE_2 has diverse and contrasting effects in myocardial remodeling, depending on which receptor subtype is activated and which cell type is involved (Table 7).

PGE_2 IN VASCULAR REMODELING

In the vasculature, PGE_2 is synthetized by ECs, VSMCs, and fibroblasts by cPGES and mPGES-2 at baseline and by mPGES-1 after an insult.[164]

Human symptomatic atherosclerotic plaques exhibit increased COX-2 and mPGES-1 expression, which likely facilitates macrophage infiltration into the plaque shoulder.[165,166] Vulnerable plaques express preferentially EPr4.[167]

In hyperlipidemic mice, deletion of mPGES-1 globally or in myeloid cells retards atherosclerosis in

Table 7. In Vivo Preclinical Studies Assessing the Effect of Prostaglandin E_2 in Cardiac Remodeling

Species	Intervention	Preclinical model	Phenotype	Mechanism	References
Mouse	Cox-1 deletion Ptges deletion EPr4 deletion EC EPr4 deletion	I/R	↑Infarct size ↓Cardiac function	↓Microvascular perfusion ↑Inflammation	135
Mouse	Ptges deletion	MI	↓Systolic function ↓Diastolic function ↑Cardiac hypertrophy ↑LV dilation ↓LV contractile function		136
Mouse	Bone marrow Ptges deletion	MI	↓Systolic function ↓Diastolic function ↑Cardiac hypertrophy ↑LV dilation ↑Mortality	↑Cox-1	137
Mouse	Myeloid cell Ptges deletion	MI	↓Mortality		138
Mouse	mPGES-1 inhibitor (CIII)	MI	↓Infarct size ↓Fibrosis	↑Urinary PGI_2/PGE_2 ratio ↓Inflammation (↓IL-1β, IL-18, TNF-α, INF-γ)	139
	Celecoxib		None		
Mouse	Ptges deletion+IPr antagonist	MI	↓Mortality ↑Infarct size		140
Mouse	EPr2 deletion	MI	↑Infarct size ↑Cardiac hypertrophy ↓Cardiac function	↓Inflammation	141
Mouse	Myeloid EPr3 deletion	MI	↓Cardiac function	↓Inflammation ↓Angiogenesis ↓TGF-β1–mediated cardiac repair	142
Mouse	Cardiomyocyte EPr3 overexpression	MI	↓Cardiac function ↑Cardiac hypertrophy ↑Cardiac fibrosis		143
Mouse	EPr3 overexpression		↓Cardiac function ↑Cardiac hypertrophy ↑Cardiac fibrosis	↑Calcineurin activity ↑NFAT activity	144
Rat Rabbit	EPr3 agonist (ONO-AE-248)	I/R	↓Infarct size	Activation of PKC Opening of K_{ATP} channels	145
Minipig	EPr3 agonist (M&B 28.767)	I/R	↓Infarct size ↓Arrhythmia		146
Mouse	EPr4 deletion EPr4 agonist (4819-C)	I/R	↑Infarct size ↓Infarct size		147
Mouse	EPr4 deletion EPr4 agonist (AE1-329)	IPC+I/R I/R	No effect on infarct size ↓Infarct size ↑Cardiac function	↑Akt signaling	148
Rat	EPr4 agonist (EP4RAG)	I/R	↓Infarct size ↑Cardiac function ↓Cardiac hypertrophy ↓Cardiac fibrosis	↓MCP-1	149
Mouse	Cardiomyocyte EPr4 deletion	MI	↓Cardiac function ↓Cardiac hypertrophy ↓Cardiac fibrosis	↑Stat-3 signaling	150
Mouse	Cardiomyocyte EPr4 deletion	MI	↓Cardiac function ↓Cardiac hypertrophy ↓Cardiac fibrosis	↑Stat-3 signaling	150
Mouse	EPr4 overexpression	MI	↑Cardiac function ↓Cardiac hypertrophy ↓Cardiac fibrosis	↓Inflammation	151
Mouse	PGE_2	HF (isoproterenol)	↑Cardiac function ↓Cardiac hypertrophy ↓Cardiac fibrosis	↓TGF-β1–GRK2 cross talk	152
Mouse	Ptges deletion	Cardiac hypertrophy (Ang II)	↓Cardiac function ↑Cardiac hypertrophy ↑Cardiac fibrosis	↑Apoptosis	153

(*Continued*)

Table 7. Continued

Species	Intervention	Preclinical model	Phenotype	Mechanism	References
Mouse	Ptges deletion	HF (isoproterenol)	↓Cardiac fibrosis		154
Mouse	Ptges deletion	HFD	↓Cardiac hypertrophy ↓Cardiac fibrosis ↓Endothelial dysfunction	↓Inflammation	155
Mouse	EPr3 deletion		↓Cardiac function ↑Cardiac hypertrophy ↑Cardiac fibrosis	↓MAPK/ERK pathway ↓MMP-2 activity	156
Mouse	EPr4 deletion	HFD	↑Cardiac hypertrophy ↑Cardiac fibrosis ↓Cardiac metabolism	↓FOXO1/CD36 signaling axis	157
Mouse	Cardiomyocyte EPr4 deletion	Aging	↓Cardiac function ↑Cardiac hypertrophy ↑Cardiac fibrosis in males but not females	↑GDF-15 in the heart	158
Mouse	EPr4 agonist (ONO-0260164)	Cardiac hypertrophy (TAC)	↑Cardiac function ↓Cardiac fibrosis	↑PKA ↓TGF-β1–mediated collagen induction	159
Mouse	EPr4 agonist (ONO-0260164)	Autoimmune myocarditis	↑Cardiac function ↑LV contractility ↓Cardiac fibrosis ↓Cardiac hypertrophy	↑TIMP-3/MMP-2 axis	160
Rat	EPr4 agonist (EP4RAG)	Autoimmune myocarditis	↑Cardiac function ↓Cardiac fibrosis	↓CD4+ T cells	161
Mouse	EPr2 deletion	MI	↓Cardiac stem cell renewal ↓Cardiac regeneration		163

AKT indicates protein kinase B; Ang II, angiotensin II; Cox, cyclooxygenase; EC, endothelial cell; EPr, prostaglandin E receptor; ERK, extracellular signal-regulated kinase; FOXO, Forkhead box O; GDF-15, growth/differentiation factor 15; GRK2, G-protein–coupled receptor kinase 2; HF, heart failure; HFD, high-fat diet; I/R, ischemia/reperfusion; IL, interleukin; INF, interferon; IPC, ischemic preconditioning; IPr, prostacyclin receptor; LV, left ventricle; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MI, myocardial infarction; MMP, metalloproteinase; mPGES, microsomal prostaglandin E2 synthase; NFAT, nuclear factor of activated T cells; PGE_2, prostaglandin E2; PGI_2, prostacyclin; PKA, protein kinase A; PKC, protein kinase C; Ptges, microsomal prostaglandin E synthase-1; Stat-3, signal transducer and activator of transcription 3; TAC, transverse aortic banding; TGF-β, transforming growth factor-beta; TIMP, tissue inhibitor of metalloproteinase; and TNF-α, tumor necrosis factor-alpha.

hyperlipidemic mice,[168,169] due to rediversion to PGI_2 with a consequent reduction in oxidative stress.[169,170] In contrast, deletion of mPGES-1 in VSMCs does not influence atherogenesis.[169]

PGE_2 produced by atherosclerotic plaques can activate platelets via the EPr3. Thus, atherothrombosis induced in vivo by mechanical rupture of the plaque is drastically decreased when platelet EPr3 is deleted.[171] Deletion of EPr4, but not of EPr2, in hematopoietic cells suppresses atherosclerotic plaque formation by promoting apoptosis.[172] EPr4 deletion in myeloid cells does not impact the size or cellular composition of the atherosclerotic plaques in diabetic mice despite reducing proinflammatory cytokines.[173] In contrast, EPr4 deletion in the bone marrow has no effect on early atherogenesis but enhances local inflammation and alters lesion composition in established atherosclerosis.[174]

In addition to atherogenesis, PGE_2 also mediates vascular remodeling after injury. Deletion of mPGES-1 globally[175] or in myeloid cells attenuates neointimal hyperplasia after vascular injury,[176] while deletion of mPGES-1 in vascular cells promotes the proliferative response.[176] Global deletion of EPr3[177] or deletion of EPr4 in VSMCs[178] or EPr4 agonists[179] restricts neointima formation in injured vessels. In contrast, global deletion of EPr2,[180] deletion of EPr4 in ECs,[179] and overexpression of EPr3 globally[177] or of EPr4 in VSMCs[178] promotes neointimal hyperplasia after vascular injury.

PGE_2 is also involved in vascular remodeling during aortic aneurysm (AAA) formation. In humans, COX-2, mPGES-1, and EPr4 expression are increased in AAA compared with nondiseased areas of the vasculature.[181,182] Deletion of mPGES-1 protects against Ang II–induced AAA by reducing VSMC proliferation and oxidative stress.[183] Similarly, pharmacological inhibition or genetic deletion of EPr4 attenuates aneurysm formation in mice.[182,184,185] On the contrary, EPr4 deletion in VSMCs exacerbates aortic dissection in response to Ang II,[186] and Epr4 deletion in bone marrow cells accelerates aneurysm formation, by increasing vascular inflammation.[187] Mice overexpressing Epr4 in VSMCs present increased mortality following Ang II infusion due to AAA formation.[188]

PGE_2 also controls BP, regulating relaxation and contraction of VSMCs and vascular stiffness.

The effect of mPGES-1 deletion on BP is highly dependent on the mouse genetic background and experimental conditions. The lack of mPGES-1 does not affect BP in unchallenged mice in all genetic backgrounds that have been tested. mPGES-1 KO mice on a 129/Sv background develop hypertension in response to HSD or Ang II infusion.[189,190] mPGES-1 KO mice on a DBA/1lacJ background remain normotensive in response to low-salt diet, DOCA-salt, or Ang II.[190–192] mPGES-1 KO mice on a mixed DBA/1lacJ×C57BL/6 background do not respond to HSD,[193] but they become hypertensive after Ang II infusion.[194] Deletion of mPGES-1 in myeloid or vascular cells does not impact BP either at baseline or in a hyperlipidemic state,[176] while deletion of mPGES-1 in hemopoietic cells induces salt-induced hypertension.[195]

EPr1 KO mice are hypotensive and present a blunted pressor response to acute and chronic Ang II infusion, low-salt diet, uninephrectomy, and deoxycorticosterone acetate.[196–198] EPr1 antagonism reduces BP in hypertensive rats[196] and prevents collagen deposition and vascular stiffness in response to Ang II.[199] EPr3 deletion or antagonism blunts the pressure response to Ang II infusion.[200,201] EPr_2 KO mice present a modest hypertension on regular diet and develop profound but reversible hypertension in response to an HSD.[202] Myeloid (LysM [lysozyme 2]-Cre) EPr4 KO mice are normotensive on a regular diet and in response to dietary sodium changes or Ang II infusion,[203] but macrophage (CD11b-Cre) EPr4 KO mice develop hypertension in response to HSD. Deletion of EPr4 in bone marrow cells evokes salt-sensitive hypertension.[187] SMC EPr4 KO mice present elevated BP in response to Ang II.[188] EC EPr4 KO mice are hypertensive, while mice overexpressing EPr4 in ECs are hypotensive both at baseline and in response to Ang II.[204]

In humans, mPGES-1 expression in abdominal fat positively correlates with systolic BP, intima-media thickness, and vascular stiffness.[155] Consistently, mPGES-1 deletion prevents cardiomyocyte hypertrophy, cardiac fibrosis, endothelial dysfunction, and vascular inflammation in mice on a high-fat diet, indicating a role for mPGES-1–dependent PGE_2 in obesity-induced vascular remodeling.[155]

Overall, these data are consistent with a direct role of PGE_2 in vascular remodeling in response to Ang II, HSD, or high-fat diet (Table 8). The conflicting results of the preclinical studies likely reflect the divergent signaling activated by the different EPrs under different experimental conditions. mPGES-1 or EPr4 may represent potential therapeutic targets for the prevention or mitigation of maladaptive vascular remodeling.

$PGF_{2\alpha}$ IN THE CARDIOVASCULAR SYSTEM

$PGF_{2\alpha}$ is synthesized by the action of PGFS (PGF_2 synthase) acting on PGH_2 and from PGD_2 and PGE_2 by cytosolic PGD_2 11-ketoreductase and PGE_2 9-ketoreductase, respectively.[3] $PGF_{2\alpha}$ exerts its effects via binding the FPr, but it can also activate TPr at high concentrations.[3]

The SNP rs10508293 in the gene encoding for $PGF_{2\alpha}$ synthase, *AKR1C3* (aldo-keto reductase family 1 member C3), is associated with reduced risk for preeclampsia.[205] The *PTGFR* rs12731181 SNP AA genotype is associated with higher FPr expression in leukocytes and increased risk for essential hypertension in a Han Chinese population.[206]

In summary, these initial genome-wide association studies indicate a deleterious effect of $PGF_{2\alpha}$ signaling in the cardiovascular system.

$PGF_{2\alpha}$ IN MYOCARDIAL REMODELING

In the heart, $PGF_{2\alpha}$ biosynthesis increases under stress conditions like hypoxia and hemodynamic stress.[207,208]

The expression of AKR1C3 in blood cells is altered in patients with MI,[209,210] and AKR1C3 may regulate ferroptosis in the cardiomyocytes of patients who experience an MI.[209]

$PGF_{2\alpha}$ levels are increased in patients with MI after percutaneous coronary intervention.[211]

The FPr is expressed in the myocardium,[212] and its activation increases contractile force and has a trophic and a positive inotropic effect in both neonatal and adult rat cardiomyocytes, through both calcium-dependent or independent mechanisms.[213] However, depending on the experimental conditions, $PGF_{2\alpha}$ can also have a negative ionotropic effect on cardiomyocytes.[214] FPr activation increases the biosynthesis of ANP (atrial natriuretic peptide) in cardiac muscle cells[215] and of collagen in the cardiac fibroblast through a mechanism independent of TGF-β.[216]

In mice, deletion of Cox-2 in cardiomyocytes induces Cox-2 expression in cardiac fibroblasts, thereby augmenting $PGF_{2\alpha}$ formation and contributing to myocardial fibrosis and arrhythmogenesis observed in these mice.[32] Rats treated with a $PGF_{2\alpha}$ analog exhibit cardiac hypertrophy and higher ANP levels.[215] FPr silencing reduces collagen expression and ameliorates myocardial fibrosis and cardiomyopathy in diabetic rats.[217] FPr deletion, similar to TPr deletion, reduces inflammatory tachycardia in mice.[112]

Overall, these investigations provide initial evidence for a harmful effect of $PGF_{2\alpha}$ in myocardial remodeling; however, additional studies in genetically modified mice lacking Akr1c3 or FPr are warranted (Table 9).

$PGF_{2\alpha}$ IN VASCULAR REMODELING

FPr is expressed in the endothelium and in VSMCs, and its expression in the vasculature increases with aging.[218] FPr silencing improves age-related hypertension,

Table 8. In Vivo Preclinical Studies Assessing the Effect of Prostaglandin E_2 in Vascular Remodeling

Species	Intervention	Preclinical model	Phenotype	Mechanism	References
Mouse	Ptges deletion	Atherosclerosis (Ldlr KO)	↓Athero plaque formation	↑PGIM ↓PGEM	168
Mouse	Myeloid cell Ptges deletion	Atherosclerosis (Ldlr KO)	↓Athero plaque formation	↓Oxidative stress	169
	VSMC Ptges deletion		None		
Mouse	IPr and Ptges deletion	Atherosclerosis (Ldlr KO)	↓Athero plaque formation	↓PGEM	170
Mouse	Platelet EPr3 deletion	Atherosclerosis (ApoE KO)	↓Atherothrombosis		171
Mouse	Hematopoietic EPr2 deletion	HFD	None	↓PI3K/Akt and NF-κB pathways	172
	Hematopoietic EPr4 deletion		↓Athero plaque formation		
Mouse	Myeloid cell EPr4 deletion	T1DM-accelerated atherogenesis	None		173
Mouse	Bone marrow EPr4 deletion	Atherosclerosis (Ldlr KO)	No effect on athero plaque size Increased inflammatory cell infiltration	↑MCP-1 ↑INF-γ	174
Mouse	Ptges deletion	Femoral injury	↓Neointimal area ↓Vascular stenosis	↓Tenascin-C	175
Mouse	VSMC Ptges deletion	Femoral injury	↑Neointimal area	↑Tenascin-C	176
	Myeloid Ptges deletion		↓Neointimal area		
Mouse	Cox-2 deletion EPr3 deletion	Femoral injury	↓Neointimal area ↓Vascular stenosis	↓Phosphatidylinositol 3-kinase signaling	177
	Epr3 overexpression Cox-1>Cox-2		↑Neointimal area ↑Vascular stenosis		
Mouse	VSMC EPr4 deletion	Femoral injury	↓Neointimal area		178
	VSMC EPr4 overexpression		↑Neointimal area	↑Tenascin-C-PKA-mTORC1-rpS6	
Mouse	IPr/Ptges deletion EC EPr4 deletion	Femoral injury	↑Neointimal area		179
	EPr4 agonist (AE1-329; misoprostol)		↓Neointimal area		
Mouse	EPr2 deletion	Femoral injury	↑Neointimal area	↑Cyclin D1 ↑PDGF-BB signaling	180
Mouse	EPr4 antagonist (ONO-AE3-208) Partial EPr4 deletion	Aneurysm formation (ApoE KO+Ang II)	↓Aneurysm formation	↓MMP activity	182
Mouse	Ptges deletion	Aneurysm formation (Ldlr KO+Ang II)	↓Aneurysm formation	↓Oxidative stress	183
Mouse	EPr4 antagonist (ONO-AE3-208)	Aneurysm formation (ApoE KO+Ang II)	↓Aneurysm formation No effect on atherogenesis	↓MMP activity ↓MIP-1α	184
	Cox-2 KD		No effect		
Mouse	EPr4 antagonist (CJ-42794)	Aneurysm formation (ApoE KO+Ang II) Aneurysm formation (ApoE KO+$CaCl_2$)	↓Aneurysm formation	↓MMP-2 activity ↓ IL-6	185
Mouse	VSMC EPr4 deletion	Aortic dissection model (Ang II)	↑BP ↑Aortic dissection	↑Vascular inflammation ↑MMP activity	186
Mouse	Bone marrow EPr4 deletion	Aneurysm formation (Ldlr KO+Ang II)	↑BP ↑Aneurysm formation	↑Vascular inflammation (↑MCP-1; apoptosis; elastin fragmentation)	187
Mouse	VSMC EPr4 overexpression	Aneurysm formation (ApoE KO+Ang II)	↑Aneurysm formation ↑Mortality	↑MMP-9 activity ↑IL-6	188
	VSMC EPr4 deletion	Aneurysm formation (Ang II or $CaCl_2$)	↑BP ↓Aneurysm formation		
Mouse	Ptges deletion (DBA/1lacJ×C57BL/6)	HSD Ang II	↑BP	NO/cGMP pathway	189

(*Continued*)

Table 8. Continued

Species	Intervention	Preclinical model	Phenotype	Mechanism	References
Mouse	Ptges deletion (DBA/1lacJ)	Unchallenged Hypertension (Ang II)	Normotensive Mild hypertension		190
	Ptges deletion (129/SvEv)	Unchallenged Hypertension (Ang II)	Slightly hypertensive Severe hypertension	↑TxBM	
Mouse	Ptges deletion	Hypertension (DOCA-salt)	↑BP	↑Oxidative stress	192
Mouse	Cox-2 deletion Cox-2 inhibition IPr deletion	Vascular damage Hypertension (Ang II)	↑Thrombogenesis ↑BP		193
	Ptges deletion (DBA/1lacJ× C57BL/6)		No effect		
Mouse	Ptges deletion (DBA/1lacJ×C57BL/6)	Hypertension (Ang II)	↑BP	↑Oxidative stress	194
Mouse	Bone marrow Cox-2 deletion Bone marrow Ptges deletion	Hypertension (HSD)	↑BP	↑Renal inflammation	195
Rat	EPr1 antagonist (SC51322) EPr1 deletion	Spontaneously hypertensive rat Hypertension (Ang II)	↓BP		196
Mouse			↓BP		
Mouse	EPr1 deletion	Regular chow LSD	↓BP		197
Mouse	EPr1 deletion	Hypertension (uninephrectomy, DOCA, Ang II)	↓BP ↓Mortality		198
Rat	Celecoxib EPr1 antagonist (SC19220)	Spontaneously hypertensive rat	↓Vascular stiffness ↓Vascular dysfunction	↓Vascular inflammation	199
Mouse		Hypertension (Ang II)			
Mouse	Epr3 deletion	Hypertension (Ang II)	↓BP both at baseline and after Ang II	↓Intracellular Ca^{2+}	200
Mouse	Epr3 antagonist (L798,106)	Hypertension (Ang II)	↓BP ↑Cardiac function		201
Mouse	Epr2 deletion	Regular chow Hypertension (HSD)	↑BP		202
Mouse	Macrophage Epr4 deletion	Hypertension (HSD, Ang II)	Normotensive		203
	Kidney epithelial cell Epr4 deletion	Hypertension (HSD) Hypertension (Ang II)	Normotensive ↑BP	↓Natriuresis	
Mouse	EC Epr4 deletion	Regular chow HSD	↑BP	↓NO ↓eNOS phosphorylation at Ser1177	204
	EC Epr4 overexpression	Regular chow HSD	↓BP		
Mouse	Ptges deletion	HFD	↓Body weight ↓Adiposity ↓Endothelial dysfunction		155

Akt indicates protein kinase B; Ang II, angiotensin II; Athero, atherosclerosis; BP, blood pressure; $CaCl_2$, calcium chloride; Cox, cyclooxygenase; DOCA, deoxycorticosterone acetate; EC, endothelial cell; eNOS, endothelial NO synthase; EPr, prostaglandin E receptor; HFD, high-fat diet; HSD, high-salt diet; IL, interleukin; INF, interferon; IPr, prostacyclin receptor; KD, knockdown; KO, knockout; Ldlr, low-density lipoprotein receptor; LSD, low-salt diet; MCP-1, monocyte chemoattractant protein-1; MIP, macrophage inflammatory protein; MMP, metalloproteinase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa B; PDGF, platelet derived growth factor; PGEM, urinary prostaglandin E metabolite; PGIM, urinary prostacyclin metabolite; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; Ptges, microsomal prostaglandin E synthase-1; T1DM, type 1 diabetes; TGF-β, transforming growth factor-beta; TxBM, urinary thromboxane metabolite synthase; and VSMC, vascular smooth muscle cell.

vascular fibrosis, and oxidative stress by preventing the upregulation of the Src/PAI-1 signal pathway.[219]

FPr deletion reduces BP after Ang II or $PGF_{2\alpha}$ infusion and retards atherosclerosis through the impairment of the renin-angiotensin-aldosterone system.[220] Moreover, FPr dimerizes with the Ang II type 1 receptor in VSMCs, contributing to the regulation of BP.[221]

In rats, FPr silencing protects from diabetes-induced vascular remodeling, causing a reduction of medial thickness, collagen content, and elastin/collagen ratio.[222]

As for myocardial remodeling, additional in vivo studies are required to understand more completely the effect of $PGF_{2\alpha}$ in vascular remodeling (Table 10).

PGD_2 IN THE CARDIOVASCULAR SYSTEM

PGD_2 is synthetized by hematopoietic- and lipocalin-type PGD_2 synthases (H-PGDS [hematopoietic PGD_2 synthase] and L-PGDS [lipocalin PGD_2 synthase], respectively).[3] H-PGDS is localized to the cytosol of

Table 9. In Vivo Preclinical Studies Assessing the Effect of Prostaglandin $F_{2\alpha}$ in Cardiac Remodeling

Species	Intervention	Preclinical model	Phenotype	Mechanism	References
Rat	$PGF_{2\alpha}$ analog (fluprostenol)		↑Cardiac hypertrophy		215
Rat	FPr shRNA	Type 2 diabetes (HFD+streptozotocin)	↓Lipids ↓Glucose ↓Insulin ↓Collagen	↓PKC/Rho and Akt signaling	217
Mouse	TPr deletion FPr deletion	Inflammatory tachycardia (LPS)	↓Tachycardia		112

Akt indicates protein kinase B; FPr, prostaglandin F receptor; HFD, high-fat diet; LPS, lipopolysaccharide; $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$; PKC, protein kinase C; and TPr, thromboxane receptor.

immune and inflammatory cells, whereas L-PGDS is expressed in several tissues and is secreted in the blood.[223] L-PGDS, in addition to its enzymatic activity, functions as a carrier of extracellular lipophilic ligands, playing an important role in metabolism.[224] PGD_2 biological activities are mediated through DPr1 and DPr2 or CRTH2 (chemoattractant receptor-homologous molecule expressed on T helper type 2 cells). 15-d (15-deoxy)-PGJ_2 is a metabolite of PGD_2 that binds DPr2 and, at orders of magnitude greater concentrations than its endogenous concentration, it also binds and activates PPARγ (peroxisome proliferator-activated receptor gamma).[3] The common SNP 111 A>C in the gene encoding for *L-PGDS* is associated with lower HDL (high-density lipoprotein) levels and higher risk for carotid atherosclerosis in Japanese patients with hypertension.[225] There are human genetic variants for DPr1 and DPr2, but they are not associated with CVD, but rather with asthma and allergic disease, indicating the important role of PGD_2 as an immune regulator. Analysis of patients with sepsis revealed that although PGD_2 is elevated in patients with sepsis of bacterial or viral origin, it has a relative selectivity for sepsis induced by SARS-CoV-2.[226] Indeed, genetic deletion or pharmacological inhibition of DPr1 protects aged mice from lethal SARS-CoV-2 infection.[227]

PGD_2 IN MYOCARDIAL REMODELING

In humans, *L-PGDS* gene expression is upregulated in the blood of infarcted patients[228] and L-PGDS levels correlate with the severity of coronary artery disease.[229] Serum L-PGDS levels increase after coronary angioplasty and negatively correlate with the reoccurrence of restenosis.[230]

Also in mice, the expression of L-PGDS in the myocardium is increased under stress conditions like chronic hypoxemia[231] and PGD_2 levels in plasma are reportedly elevated after MI.[232] L-PGDS–derived PGD_2 mediates the protective effect of glucocorticoids against myocardial I/R injury by the activation of the PGD_2-DPr1-ERK1/2 (extracellular signal-regulated kinase 1/2) signaling pathway[233] or the transcription factor Nrf2 (nuclear factor erythroid 2-related factor 2) via FPr.[234] Deletion of DPr1 in macrophages retards cardiac healing after MI by impairing M2 polarization and, therefore, the resolution of the inflammation post-MI.[235] Genetic deletion of DPr2 or DPr2 antagonism protects against MI by reducing ER stress–induced cardiomyocyte apoptosis.[236] In contrast, DPr2 deficiency in fibroblasts exacerbates isoproterenol-induced myocardial fibrosis since ER-anchored DPr2 promotes collagen degradation in fibroblasts via binding to La ribonucleoprotein domain family member 6.[237]

Overall, DPr2 expressed on cardiomyocytes or cardiac fibroblasts has a divergent effect (Table 11). Antagonizing DPr2 on cardiomyocytes may prevent ischemia-induced apoptosis in the heart. In contrast, DPr2 activation on fibroblasts may suppress stress-induced organ fibrosis.

More studies are required to unveil the role of DPr1 in myocardial remodeling.

PGD_2 IN VASCULAR REMODELING

L-PGDS levels are increased in patients with essential hypertension and in patients with hypertension with atrial fibrillation.[238,239] Moreover, L-PGDS is expressed on the atherosclerotic plaque and its serum level correlates with the severity of coronary artery disease.[229] Hyperlipidemic L-Pgds KO mice develop metabolic syndrome, fat deposition, thickening of the aortic media,[240] and

Table 10. In Vivo Preclinical Studies Assessing the Effect of Prostaglandin $F_{2\alpha}$ in Vascular Remodeling

Species	Intervention	Preclinical model	Phenotype	Mechanism	References
Mouse	FPr deletion	Atherosclerosis (Ldlr KO)	↓Athero plaque formation ↓BP	↓Inflammation (TNF-α; iNOS; TGF-β, macrophages) ↓Renin, angiotensin, and aldosterone	220
Rat	FPr shRNA	Type 2 diabetes (HFD+streptozotocin)	↓Medial thickness, collagen content, elastin/collagen ratio	↓JNK phosphorylation	222

Athero indicates atherosclerosis; BP, blood pressure; FPr, prostaglandin F receptor; HFD, high-fat diet; iNOS, inducible NO synthase; JNK, c-Jun N-terminal kinase; KO, knockout; Ldlr, low-density lipoprotein receptor; TGF-β, transforming growth factor-beta; and TNF-α, tumor necrosis factor-alpha.

Table 11. In Vivo Preclinical Studies Assessing the Effect of Prostaglandin D_2 in Cardiac Remodeling

Species	Intervention	Preclinical model	Phenotype	Mechanism	References
Mouse	Ptgds deletion+dexamethasone	I/R	Loss of cardioprotective effect	↓ERK1/2 signaling	233
Mouse	FPr deletion+dexamethasone	I/R	Loss of cardioprotective effect	↓NRF-2 signaling	234
Mouse	Macrophage DPr1 deletion	MI	↓Cardiac function ↑Infarct size	↓JAK2/STAT1 signaling ↓Macrophage M2 polarization ↓Inflammation resolution	235
Mouse	DPr2 deletion DPr2 antagonist (CAY10595)	MI	↑Cardiac function ↓Infarct size ↓Fibrosis ↓Hypertrophy ↓Mortality	↓ER stress-induced cardiomyocyte apoptosis ↓Caspase-12	236
Mouse	Fibroblast DPr2 deletion	Isoproterenol	↑Fibrosis	↓Reduced binding to La ribonucleoprotein domain family member 6	237

DPr indicates prostaglandin D receptor; ER, endoplasmic reticulum; ERK1/2, extracellular signal-regulated kinase 1/2; FPr, prostaglandin F receptor; I/R, ischemia/reperfusion; JAK2, Janus kinase 2; MI, myocardial infarction; NRF-2, nuclear factor erythroid 2-related factor 2; Ptgds, lipocalin prostaglandin d synthase; and STAT1, signal transducer and activator of transcription 1.

accelerated atherosclerosis due to an increased inflammatory response.[241] Moreover, L-Pgds, but not H-Pgds, deletion accelerates thrombogenesis and evokes hypertension, due to its function as lipophilic carrier.[242] In neurogenic hypertensive rats, inhibition of L-PGDS reduces, whereas DPr1 antagonism augments Ang II-salt–induced hypertension.[243]

ApoE DPr1 KO mice infused with Ang II exhibit increased AAA formation and an exaggerated BP response. They also have accelerated atherogenesis

Table 12. In Vivo Preclinical Studies Assessing the Effect of Prostaglandin D_2 in Vascular Remodeling

Species	Intervention	Preclinical model	Phenotype	Mechanism	References
Mouse	Ptgds deletion	HFD	↑Glucose intolerant ↑Insulin resistant ↑Athero plaque formation ↑Aortic thickening		240
Mouse	Ptgds deletion	Atherosclerosis (ApoE KO+HFD)	↑Body weight ↑Athero plaque formation	↑Macrophage infiltration ↑Inflammation (IL-1β, MCP-1)	241
Mouse	Ptgds deletion		↑BP ↑Thrombogenesis		242
	H-Pgds deletion		None		
Rat	COX inhibitor Ptgds inhibitor (AT56)	Hypertension (HSD+Ang II)	↓BP		243
	DPr1 antagonist (BWA868C)		↑BP		
Mouse	DPr1 deletion	Atherosclerosis (ApoE KO) Aneurism formation (ApoE KO+Ang II)	↑Athero plaque formation ↑Aneurysm formation ↓Thrombogenesis (female mice)		244
Mouse	VSMC DPr1 deletion	Hypertension (Ang II)	↑BP ↑Vascular media thickness	↑VSMC switch to myofibroblasts by impairing ↓Phosphorylation of MRTF by ROCK-1	245
Mouse	DPr1 deletion DPr1 antagonist (laropiprant) DPr2 antagonist (fevipiprant)	Aneurism formation (Ang II+$CaCl_2$)	↓Aneurism formation	↓MMP ↓Elastin degradation ↓Inflammation	246
Mouse	$CD4^+$ T-cell DPr1 deletion	Aging	↑BP		247
	$CD4^+$ T-cell DPr1 overexpression		↓BP	↓Th1 activation ↑NEDD4L-mediated T-bet degradation	

Ang II indicates angiotensin II; Athero, atherosclerosis; BP, blood pressure; $CaCl_2$, calcium chloride; COX, cyclooxygenase; DPr, prostaglandin D receptor; HFD, high-fat diet; H-PGDS, hematopoietic prostaglandin D synthase; HSD, high-salt diet; IL, interleukin; KO, knockout; MCP-1, monocyte chemoattractant protein-1; MMP, metalloproteinase; MRTF, myocardin-related transcription factor; NEDD4L, neural precursor cell expressed developmentally downregulated gene 4-like; Ptgds, lipocalin prostaglandin D synthase; ROCK-1, Rho-associated kinase-1; Th1, type 1 T helper cells; and VSMC, vascular smooth muscle cell.

and thrombogenesis.[244] Because mouse platelets do not express DPr1, these phenotypes are a consequence of the lack of DPr1 in the vasculature. Consistently, deletion of DPr1 in VSMCs evokes hypertension and thickening of the vasculature after Ang II infusion, due to the lack of a protective role of DPr1 on VSMC phenotypic switching to myofibroblasts.[245] Genetic deletion of DPr1 or antagonism of DPr1 or DPr2 protects against Ang II–induced and calcium chloride–induced AAA.[246] Deletion of DPr1 in CD^{4+} T cells aggravates, whereas DPr1 overexpression in CD^{4+} T cells retards age-induced hypertension by modulating vascular/renal superoxide production in male mice.[247]

In summary, DPr1 may serve as a target for reducing age-related vascular diseases, including hypertension, atherosclerosis, and AAA (Table 12).

CONCLUSIONS

Prostanoids play a complex and essential role in regulating myocardial and vascular remodeling.

In addition to increasing the risk of atherothrombotic events, prostanoid inhibition by NSAIDs may favor adverse remodeling of the cardiovascular system, contributing to the nonischemic cardiovascular complications associated with the use of these drugs.

Nevertheless, increasing evidence supports the potential therapeutic value of targeting prostanoid synthases or their receptors for the treatment of CVD. Further studies in suitable animal models of human relevance, including age and sex as variables, are required to advance the rationale for clinical development of effective therapeutic strategies to prevent or mitigate adverse cardiovascular remodeling.

ARTICLE INFORMATION

Received August 22, 2023; accepted January 9, 2024.

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Sources of Funding

This work was supported by the National Institutes of Health/National Heart, Lung, and Blood Institute R01 HL141912 (to G.A. FitzGerald).

Disclosures

None.

REFERENCES

1. Smyth EM, Grosser T, Wang M, Yu Y, Fitzgerald GA. Prostanoids in health and disease. *J Lipid Res*. 2009;50:S423–S428. doi: 10.1194/jlr.R800094-JLR200
2. Sellers RS, Radi ZA, Khan NK. Pathophysiology of cyclooxygenases in cardiovascular homeostasis. *Vet Pathol*. 2010;47:601–613. doi: 10.1177/0300985810364389
3. Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. *Arterioscler Thromb Vasc Biol*. 2011;31:986–1000. doi: 10.1161/ATVBAHA.110.207449
4. FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *N Engl J Med*. 2001;345:433–442. doi: 10.1056/NEJM200108093450607
5. Grosser T, Yu Y, Fitzgerald GA. Emotion recollected in tranquility: lessons learned from the COX-2 saga. *Annu Rev Med*. 2010;61:17–33. doi: 10.1146/annurev-med-011209-153129
6. Bhala N, Emberson J, Merhi A, Abramson S, Arber N, Baron JA, Bombardier C, Cannon C, Farkouh ME, FitzGerald GA, et al; Coxib and Traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomizedsed trials. *Lancet*. 2013;382:769–779. doi: 10.1016/S0140-6736(13)60900-9
7. MacDonald TM, Hawkey CJ, Ford I, McMurray JJV, Scheiman JM, Hallas J, Findlay E, Grobbee DE, Hobbs FDR, Ralston SH, et al. Randomized trial of switching from prescribed non-selective non-steroidal anti-inflammatory drugs to prescribed celecoxib: the Standard Care vs Celecoxib Outcome Trial (SCOT). *Eur Heart J*. 2017;38:1843–1850. doi: 10.1093/eurheartj/ehw387
8. Nissen SE, Yeomans ND, Solomon DH, Lüscher TF, Libby P, Husni ME, Graham DY, Borer JS, Wisniewski LM, Wolski KE, et al; PRECISION Trial Investigators. PRECISION trial investigators cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. *N Engl J Med*. 2016;375:2519–2529. doi: 10.1056/NEJMoa1611593
9. Barcella CA, Lamberts M, McGettigan P, Fosbøl EL, Lindhardsen J, Torp-Pedersen C, Gislason GH, Olsen AS. Differences in cardiovascular safety with non-steroidal anti-inflammatory drug therapy—a nationwide study in patients with osteoarthritis. *Basic Clin Pharmacol Toxicol*. 2019;124:629–641. doi: 10.1111/bcpt.13182
10. Azevedo PS, Polegato BF, Minicucci MF, Paiva SA, Zornoff LA. Cardiac remodeling: concepts, clinical impact, pathophysiological mechanisms and pharmacologic treatment. *Arq Bras Cardiol*. 2016;106:62–69. doi: 10.5935/abc.20160005
11. Maree AO, Curtin RJ, Chubb A, Dolan C, Cox D, O'Brien J, Crean P, Shields DC, Fitzgerald DJ. Cyclooxygenase-1 haplotype modulates platelet response to aspirin. *J Thromb Haemost*. 2005;3:2340–2345. doi: 10.1111/j.1538-7836.2005.01555.x
12. Clappers N, van Oijen MG, Sundaresan S, Brouwer MA, Te Morsche RH, Keuper W, Peters WH, Drenth JP, Verheugt FW. The C50T polymorphism of the cyclooxygenase-1 gene and the risk of thrombotic events during low-dose therapy with acetyl salicylic acid. *Thromb Haemost*. 2008;100:70–75. doi: 10.1160/TH08-03-0172
13. Helmersson J, Arnlov J, Axelsson T, Basu S. A polymorphism in the cyclooxygenase 1 gene is associated with decreased inflammatory prostaglandin F2alpha formation and lower risk of cardiovascular disease. *Prostaglandins Leukot Essent Fatty Acids*. 2009;80:51–56. doi: 10.1016/j.plefa.2008.11.001
14. Cao L, Zhang Z, Sun W, Bai W, Sun W, Zhang Y, Wang X, Cai B, Xie X, Duan Z, et al. Impacts of COX-1 gene polymorphisms on vascular outcomes in patients with ischemic stroke and treated with aspirin. *Gene*. 2014;546:172–176. doi: 10.1016/j.gene.2014.06.023
15. Zheng H, Fu L, Xu Y, Zhang TF, Che D, Li JQ, Zhou H, Jiang Z, Lin K, Zhang L, et al. The PTGS1 (rs1330344) CC genotype contributes to susceptibility to Kawasaki disease in southern Chinese children. *Angiology*. 2023;74:832–839. doi: 10.1177/00033197221118343
16. Papafili A, Hill MR, Brull DJ, McAnulty RJ, Marshall RP, Humphries SE, Laurent GJ. Common promoter variant in cyclooxygenase-2 represses gene expression: evidence of role in acute-phase inflammatory response. *Arterioscler Thromb Vasc Biol*. 2002;22:1631–1636. doi: 10.1161/01.atv.0000030340.80207.c5
17. Orbe J, Beloqui O, Rodriguez JA, Belzunce MS, Roncal C, Páramo JA. Protective effect of the G-765C COX-2 polymorphism on subclinical atherosclerosis and inflammatory markers in asymptomatic subjects with cardiovascular risk factors. *Clin Chim Acta*. 2006;368:138–143. doi: 10.1016/j.cca.2005.12.019
18. Cipollone F, Toniato E, Martinotti S, Fazia M, Iezzi A, Cuccurullo C, Pini B, Ursi S, Vitullo G, Averna M, et al; Identification of New Elements of Plaque Stability (INES) Study Group. A polymorphism in the cyclooxygenase 2 gene as an inherited protective factor against myocardial infarction and stroke. *JAMA*. 2004;291:2221–2228. doi: 10.1001/jama.291.18.2221
19. Xie X, Ma YT, Fu ZY, Yang YN, Ma X, Chen BD, Wang YH, Liu F. Association of polymorphisms of PTGS2 and CYP8A1 with myocardial infarction. *Clin Chem Lab Med*. 2009;47:347–352. doi: 10.1515/CCLM.2009.078

20. Kim IJ, Kim SH, Cha DH, Lim SW, Moon JY, Kim JO, Ryu CS, Park HS, Sung JH, Kim NK. Association of COX2 -765G>C promoter polymorphism and coronary artery disease in Korean population. *Genes Genomics*. 2019;41:1055–1062. doi: 10.1007/s13258-019-00835-5
21. Lee CR, North KE, Bray MS, Couper DJ, Heiss G, Zeldin DC. Cyclooxygenase polymorphisms and risk of cardiovascular events: the Atherosclerosis Risk in Communities (ARIC) study. *Clin Pharmacol Ther*. 2008;83:52–60. doi: 10.1038/sj.clpt.6100221
22. Rudock ME, Liu Y, Ziegler JT, Allen SG, Lehtinen AB, Freedman BI, Carr JJ, Langefeld CD, Bowden DW. Association of polymorphisms in cyclooxygenase (COX)-2 with coronary and carotid calcium in the diabetes heart study. *Atherosclerosis*. 2009;203:459–465. doi: 10.1016/j.atherosclerosis.2008.07.018
23. Ross S, Eikelboom J, Anand SS, Eriksson N, Gerstein HC, Mehta S, Connolly SJ, Rose L, Ridker PM, Wallentin L, et al. Association of cyclooxygenase-2 genetic variant with cardiovascular disease. *Eur Heart J*. 2014;35:2242–228a. doi: 10.1093/eurheartj/ehu168
24. Liu H, Xu Z, Sun C, Gu D, Teng X, Zhao Y, Zheng Z. A variant in COX-2 gene is associated with left main coronary artery disease and clinical outcomes of coronary artery bypass grafting. *Biomed Res Int*. 2017;2017:2924731. doi: 10.1155/2017/2924731
25. Wang Y, Zhou Q, Gao WH, Yan Y, Chu C, Chen C, Yuan Y, Wang KK, Ma Q, Gao K, et al. Association of plasma cyclooxygenase-2 levels and genetic polymorphisms with salt sensitivity, blood pressure changes and hypertension incidence in Chinese adults. *J Hypertens*. 2020;38:1745–1754. doi: 10.1097/HJH.0000000000002473
26. Wong SC, Fukuchi M, Melnyk P, Rodger I, Giaid A. Induction of cyclooxygenase-2 and activation of nuclear factor-kappaB in myocardium of patients with congestive heart failure. *Circulation*. 1998;98:100–103. doi: 10.1161/01.cir.98.2.100
27. Kim JW, Baek BS, Kim YK, Herlihy JT, Ikeno Y, Yu BP, Chung HY. Gene expression of cyclooxygenase in the aging heart. *J Gerontol A Biol Sci Med Sci*. 2001;56:B350–B355. doi: 10.1093/gerona/56.8.b350
28. Camitta MG, Gabel SA, Chulada P, Bradbury JA, Langenbach R, Zeldin DC, Murphy E. Cyclooxygenase-1 and -2 knockout mice demonstrate increased cardiac ischemia/reperfusion injury but are protected by acute preconditioning. *Circulation*. 2001;104:2453–2458. doi: 10.1161/hc4401.098429
29. Ling QL, Mohite AJ, Murdoch E, Akasaka H, Li QY, So SP, Ruan KH. Creating a mouse model resistant to induced ischemic stroke and cardiovascular damage. *Sci Rep*. 2018;8:1653. doi: 10.1038/s41598-018-19661-y
30. Dinchuk JE, Car BD, Focht RJ, Johnston JJ, Jaffee BD, Covington MB, Contel NR, Eng VM, Collins RJ, Czerniak PM, et al. Renal abnormalities and an altered inflammatory response in mice lacking cyclooxygenase II. *Nature*. 1995;378:406–409. doi: 10.1038/378406a0
31. Wan Q, Kong D, Liu Q, Guo S, Wang C, Zhao Y, Ke ZJ, Yu Y. Congestive heart failure in COX2 deficient rats. *Sci China Life Sci*. 2021;64:1068–1076. doi: 10.1007/s11427-020-1792-5
32. Wang D, Patel VV, Ricciotti E, Zhou R, Levin MD, Gao E, Yu Z, Ferrari VA, Lu MM, Xu J, et al. Cardiomyocyte cyclooxygenase-2 influences cardiac rhythm and function. *Proc Natl Acad Sci USA*. 2009;106:7548–7552. doi: 10.1073/pnas.0805806106
33. Inserte J, Molla B, Aguilar R, Través PG, Barba I, Martín-Sanz P, Boscá L, Casado M, Garcia-Dorado D. Constitutive COX-2 activity in cardiomyocytes confers permanent cardioprotection. *J Mol Cell Cardiol*. 2009;46:160–168. doi: 10.1016/j.yjmcc.2008.11.011
34. Guo Y, Nong Y, Tukaye DN, Rokosh G, Du J, Zhu X, Book M, Tomlin A, Li Q, Bolli R. Inducible cardiac-specific overexpression of cyclooxygenase-2 (COX-2) confers resistance to ischemia/reperfusion injury. *Basic Res Cardiol*. 2019;114:32. doi: 10.1007/s00395-019-0741-2
35. Streicher JM, Kamei K, Ishikawa TO, Herschman H, Wang Y. Compensatory hypertrophy induced by ventricular cardiomyocyte-specific COX-2 expression in mice. *J Mol Cell Cardiol*. 2010;49:88–94. doi: 10.1016/j.yjmcc.2010.01.021
36. Thai PN, Ren L, Xu W, Overton J, Timofeyev V, Nader CE, Haddad M, Yang J, Gomes AV, Hammock BD, et al. Chronic diclofenac exposure increases mitochondrial oxidative stress, inflammatory mediators, and cardiac dysfunction. *Cardiovasc Drugs Ther*. 2023;37:25–37. doi: 10.1007/s10557-021-07253-4
37. Saito T, Rodger IW, Hu F, Robinson R, Huynh T, Giaid A. Inhibition of COX pathway in experimental myocardial infarction. *J Mol Cell Cardiol*. 2004;37:71–77. doi: 10.1016/j.yjmcc.2004.04.002
38. LaPointe MC, Mendez M, Leung A, Tao Z, Yang XP. Inhibition of cyclooxygenase-2 improves cardiac function after myocardial infarction in the mouse. *Am J Physiol Heart Circ Physiol*. 2004;286:H1416–H1424. doi: 10.1152/ajpheart.00136.2003
39. Zhang C, Wang F, Zhang Y, Kang Y, Wang H, Si M, Su L, Xin X, Xue F, Hao F, et al. Celecoxib prevents pressure overload-induced cardiac hypertrophy and dysfunction by inhibiting inflammation, apoptosis and oxidative stress. *J Cell Mol Med*. 2016;20:116–127. doi: 10.1111/jcmm.12709
40. Adamek A, Hu K, Bayer B, Wagner H, Ertl G, Bauersachs J, Frantz S. High dose aspirin and left ventricular remodeling after myocardial infarction: aspirin and myocardial infarction. *Basic Res Cardiol*. 2007;102:334–340. doi: 10.1007/s00395-007-0647-2
41. Shinmura K, Tang XL, Wang Y, Xuan YT, Liu SQ, Takano H, Bhatnagar A, Bolli R. Cyclooxygenase-2 mediates the cardioprotective effects of the late phase of ischemic preconditioning in conscious rabbits. *Proc Natl Acad Sci USA*. 2000;97:10197–10202. doi: 10.1073/pnas.97.18.10197
42. Timmers L, Sluijter JPG, Verlaan CWJ, Steendijk P, Cramer MJ, Emons M, Strijder C, Grüdeman PF, Sze SK, Hua L, et al. Cyclooxygenase-2 inhibition increases mortality, enhances left ventricular remodeling, and impairs systolic function after myocardial infarction in the pig. *Circulation*. 2007;115:326–332. doi: 10.1161/CIRCULATIONAHA.106.647230
43. van der Hoorn JW, Jukema JW, Bekkers ME, Princen HM, Corda S, Emeis JJ, Steendijk P. Negative effects of rofecoxib treatment on cardiac function after ischemia-reperfusion injury in APOE3Leiden mice are prevented by combined treatment with thromboxane prostanoid-receptor antagonist S18886 (terutroban). *Crit Care Med*. 2008;36:2576–2582. doi: 10.1097/CCM.0b013e318183f0fd
44. Belton O, Byrne D, Kearney D, Leahy A, Fitzgerald DJ. Cyclooxygenase-1 and -2-dependent prostacyclin formation in patients with atherosclerosis. *Circulation*. 2000;102:840–845. doi: 10.1161/01.cir.102.8.840
45. Sef D, Kovacevic M, Jernej B, Novacic K, Slavica M, Petrak J, Medved I, Milosevic M. Immunohistochemical analysis of MMP-9 and COX-2 expression in carotid atherosclerotic plaques among patients undergoing carotid endarterectomy: a prospective study. *J Stroke Cerebrovasc Dis*. 2022;31:106731. doi: 10.1016/j.jstrokecerebrovasdis.2022.106731
46. McClelland S, Gawaz M, Kennerknecht E, Konrad CSI, Sauer S, Schuerzinger K, Massberg S, Fitzgerald DJ, Belton O. Contribution of cyclooxygenase-1 to thromboxane formation, platelet-vessel wall interactions and atherosclerosis in the ApoE null mouse. *Atherosclerosis*. 2009;202:84–91. doi: 10.1016/j.atherosclerosis.2008.04.016
47. Cyrus T, Yao Y, Ding T, Dogne JM, Pratico D. Thromboxane receptor blockade improves the antiatherogenic effect of thromboxane A2 suppression in LDLR KO mice. *Blood*. 2007;109:3291–3296. doi: 10.1182/blood-2006-08-044990
48. Belton OA, Duffy A, Toomey S, Fitzgerald DJ. Cyclooxygenase isoforms and platelet vessel wall interactions in the apolipoprotein E knockout mouse model of atherosclerosis. *Circulation*. 2003;108:3017–3023. doi: 10.1161/01.CIR.0000104565.78013.AD
49. Qi Z, Hao CM, Langenbach RI, Breyer RM, Redha R, Morrow JD, Breyer MD. Opposite effects of cyclooxygenase-1 and -2 activity on the pressor response to angiotensin II. *J Clin Invest*. 2002;110:61–69. doi: 10.1172/jci0214752
50. Babaev VR, Ding L, Reese J, Morrow JD, Breyer MD, Dey SK, Fazio S, Linton MF. Cyclooxygenase-1 deficiency in bone marrow cells increases early atherosclerosis in apolipoprotein E- and low-density lipoprotein receptor-null mice. *Circulation*. 2006;113:108–117. doi: 10.1161/CIRCULATIONAHA.105.591537
51. Mitchell JA, Shala F, Pires MEL, Loy RY, Ravendren A, Benson J, Urquhart P, Nicolaou A, Herschman HR, Kirkby NS. Endothelial cyclooxygenase-1 paradoxically drives local vasoconstriction and atherogenesis despite underpinning prostacyclin generation. *Sci Adv*. 2021;7:eabf6054. doi: 10.1126/sciadv.abf6054
52. Li S, Liu B, Luo W, Zhang Y, Li H, Huang D, Zhou Y. Role of cyclooxygenase-1 and -2 in endothelium-dependent contraction of atherosclerotic mouse abdominal aortas. *Clin Exp Pharmacol Physiol*. 2016;43:67–74. doi: 10.1111/1440-1681.12501
53. Rott D, Zhu J, Burnett MS, Zhou YF, Zalles-Ganley A, Ogunmakinwa J, Epstein SE. Effects of MF-tricyclic, a selective cyclooxygenase-2 inhibitor, on atherosclerosis progression and susceptibility to cytomegalovirus replication in apolipoprotein-E knockout mice. *J Am Coll Cardiol*. 2003;41:1812–1819. doi: 10.1016/s0735-1097(03)00304-8
54. Olesen M, Kwong E, Meztli A, Kontny F, Seljeflot I, Arnesen H, Lyngdorf L, Falk E. No effect of cyclooxygenase inhibition on plaque size in atherosclerosis-prone mice. *Scand Cardiovasc J*. 2002;36:362–367. doi: 10.1080/140174302762659094
55. Pratico D, Tillmann C, Zhang ZB, Li H, FitzGerald GA. Acceleration of atherogenesis by COX-1-dependent prostanoid formation in low density lipoprotein receptor knockout mice. *Proc Natl Acad Sci USA*. 2001;98:3358–3363. doi: 10.1073/pnas.061607398

56. Bea F, Blessing E, Bennett BJ, Kuo CC, Campbell LA, Kreuzer J, Rosenfeld ME. Chronic inhibition of cyclooxygenase-2 does not alter plaque composition in a mouse model of advanced unstable atherosclerosis. *Cardiovasc Res*. 2003;60:198–204. doi: 10.1016/s0008-6363(03)00464-4
57. Burleigh ME, Babaev VR, Oates JA, Harris RC, Gautam S, Riendeau D, Marnett LJ, Morrow JD, Fazio S, Linton MF. Cyclooxygenase-2 promotes early atherosclerotic lesion formation in LDL receptor-deficient mice. *Circulation*. 2002;105:1816–1823. doi: 10.1161/01.cir.0000014927.74465.7f
58. Burleigh ME, Babaev VR, Yancey PG, Major AS, McCaleb JL, Oates JA, Morrow JD, Fazio S, Linton MF. Cyclooxygenase-2 promotes early atherosclerotic lesion formation in ApoE-deficient and C57BL/6 mice. *J Mol Cell Cardiol*. 2005;39:443–452. doi: 10.1016/j.yjmcc.2005.06.011
59. Jacob S, Laury-Kleintop L, Lanza-Jacoby S. The select cyclooxygenase-2 inhibitor celecoxib reduced the extent of atherosclerosis in apo E-/- mice. *J Surg Res*. 2008;146:135–142. doi: 10.1016/j.jss.2007.04.040
60. Metzner J, Popp L, Marian C, Schmidt R, Manderscheid C, Renne C, Fisslthaler B, Fleming I, Busse R, Geisslinger G, et al. The effects of COX-2 selective and non-selective NSAIDs on the initiation and progression of atherosclerosis in ApoE-/- mice. *J Mol Med (Berl)*. 2007;85:623–633. doi: 10.1007/s00109-007-0162-9
61. Gong C, Qi Y, Xu Y, Tang X, Liang F, Chen L. Parecoxib improves atherosclerotic plaque stability by suppressing inflammation and inhibiting matrix metalloproteinases production. *Biomed Pharmacother*. 2021;138:111423. doi: 10.1016/j.biopha.2021.111423
62. Yu Z, Crichton I, Tang SY, Hui Y, Ricciotti E, Levin MD, Lawson JA, Puré E, Fitzgerald GA. Disruption of the 5-lipoxygenase pathway attenuates atherogenesis consequent to COX-2 deletion in mice. *Proc Natl Acad Sci USA*. 2012;109:6727–6732. doi: 10.1073/pnas.1115313109
63. Tang SY, Monslow J, Todd L, Lawson J, Pure E, FitzGerald GA. Cyclooxygenase-2 in endothelial and vascular smooth muscle cells restrains atherogenesis in hyperlipidemic mice. *Circulation*. 2014;129:1761–1769. doi: 10.1161/CIRCULATIONAHA.113.007913
64. Hui Y, Ricciotti E, Crichton I, Yu Z, Wang D, Stubbe J, Wang M, Pure E, FitzGerald GA. Targeted deletions of cyclooxygenase-2 and atherogenesis in mice. *Circulation*. 2010;121:2654–2660. doi: 10.1161/CIRCULATIONAHA.109.910687
65. Zhang K, Kong J, Liu B, Meng X. Regulatory T cells suppress the expression of COX-2 in vulnerable plaque. *Heart Vessels*. 2020;35:278–283. doi: 10.1007/s00380-019-01491-1
66. FitzGerald GA. COX-2 and beyond: approaches to prostaglandin inhibition in human disease. *Nat Rev Drug Discov*. 2003;2:879–890. doi: 10.1038/nrd1225
67. Aw TJ, Haas SJ, Liew D, Krum H. Meta-analysis of cyclooxygenase-2 inhibitors and their effects on blood pressure. *Arch Intern Med*. 2005;165:490–496. doi: 10.1001/archinte.165.5.IOI50013
68. Stæhr M, Hansen PB, Madsen K, Vanhoutte PM, Nüsing RM, Jensen BL. Deletion of cyclooxygenase-2 in the mouse increases arterial blood pressure with no impairment in renal NO production in response to chronic high salt intake. *Am J Physiol Regul Integr Comp Physiol*. 2013;304:R899–R907. doi: 10.1152/ajpregu.00103.2012
69. Yu Y, Stubbe J, Ibrahim S, Song WL, Smyth EM, Funk CD, FitzGerald GA. Cyclooxygenase-2-dependent prostacyclin formation and blood pressure homeostasis: targeted exchange of cyclooxygenase isoforms in mice. *Circ Res*. 2010;106:337–345. doi: 10.1161/CIRCRESAHA.109.204529
70. Yu Y, Ricciotti E, Scalia R, Tang SY, Grant G, Yu Z, Landesberg G, Crichton I, Wu W, Puré E, et al. Vascular COX-2 modulates blood pressure and thrombosis in mice. *Sci Transl Med*. 2012;4:132ra–13254. doi: 10.1126/scitranslmed.3003787
71. Funk CD, FitzGerald GA. COX-2 inhibitors and cardiovascular risk. *J Cardiovasc Pharmacol*. 2007;50:470–479. doi: 10.1097/FJC.0b013e318157f72d
72. Lemaitre RN, Rice K, Marciante K, Bis JC, Lumley TS, Wiggins KL, Smith NL, Heckbert SR, Psaty BM. Variation in eicosanoid genes, non-fatal myocardial infarction and ischemic stroke. *Atherosclerosis*. 2009;204:e58–e63. doi: 10.1016/j.atherosclerosis.2008.10.011
73. Nakayama T, Soma M, Saito S, Honye J, Yajima J, Rahmutula D, Kaneko Y, Sato M, Uwabo J, Aoi N, et al. Association of a novel single nucleotide polymorphism of the prostacyclin synthase gene with myocardial infarction. *Am Heart J*. 2002;143:797–801. doi: 10.1067/mhj.2002.122171
74. Yi X, Ming B, Wang C, Chen H, Ma C. Variants in COX-2, PTGIS, and TBXAS1 are associated with carotid artery or intracranial arterial stenosis and neurologic deterioration in ischemic stroke patients. *J Stroke Cerebrovasc Dis*. 2017;26:1128–1135. doi: 10.1016/j.jstrokecerebrovasdis.2016.12.032
75. Yamada Y, Matsuo H, Segawa T, Watanabe S, Kato K, Hibino T, Yokoi K, Ichihara S, Metoki N, Yoshida H, et al. Assessment of the genetic component of hypertension. *Am J Hypertens*. 2006;19:1158–1165. doi: 10.1016/j.amjhyper.2006.04.010
76. Arehart E, Stitham J, Asselbergs FW, Douville K, MacKenzie T, Fetalvero KM, Gleim S, Kasza Z, Rao Y, Martel L, et al. Acceleration of cardiovascular disease by a dysfunctional prostacyclin receptor mutation: potential implications for cyclooxygenase-2 inhibition. *Circ Res*. 2008;102:986–993. doi: 10.1161/CIRCRESAHA.107.165936
77. Patrignani P, Di Febbo C, Tacconelli S, Douville K, Guglielmi MD, Horvath RJ, Ding M, Sierra K, Stitham J, Gleim S, et al. Differential association between human prostacyclin receptor polymorphisms and the development of venous thrombosis and intimal hyperplasia: a clinical biomarker study. *Pharmacogenet Genomics*. 2008;18:611–620. doi: 10.1097/FPC.0b013e328301a774
78. Francois H, Athirakul K, Howell D, Dash R, Mao L, Kim H-S, Rockman HA, Fitzgerald GA, Koller BH, Coffman TM. Prostacyclin protects against elevated blood pressure and cardiac fibrosis. *Cell Metab*. 2005;2:201–207. doi: 10.1016/j.cmet.2005.08.005
79. Chan EC, Dusting GJ, Guo N, Peshavariya HM, Taylor CJ, Dilley R, Narumiya S, Jiang F. Prostacyclin receptor suppresses cardiac fibrosis: role of CREB phosphorylation. *J Mol Cell Cardiol*. 2010;49:176–185. doi: 10.1016/j.yjmcc.2010.04.006
80. Hara A, Yuhki K, Fujino T, Yamada T, Takayama K, Kuriyama S, Takahata O, Karibe H, Okada Y, Xiao CY, et al. Augmented cardiac hypertrophy in response to pressure overload in mice lacking the prostaglandin I2 receptor. *Circulation*. 2005;112:84–92. doi: 10.1161/CIRCULATIONAHA.104.527077
81. Xiao CY, Hara A, Yuhki K, Fujino T, Ma H, Okada Y, Takahata O, Yamada T, Murata T, Narumiya S, et al. Roles of prostaglandin I(2) and thromboxane A(2) in cardiac ischemia-reperfusion injury: a study using mice lacking their respective receptors. *Circulation*. 2001;104:2210–2215. doi: 10.1161/hc4301.098058
82. Kaneshige T, Saida Y, Tanaka R, Soda A, Fukushima A, Ida N, Takenaka M, Yamane Y. Effect of long-term administration of a prostacyclin analogue (beraprost sodium) on myocardial fibrosis in Dahl rats. *J Vet Med Sci*. 2007;69:1271–1276. doi: 10.1292/jvms.69.1271
83. Masada K, Miyagawa S, Sakai Y, Harada A, Kanaya T, Sawa Y. Synthetic prostacyclin agonist attenuates pressure-overloaded cardiac fibrosis by inhibiting FMT. *Mol Ther Methods Clin Dev*. 2020;19:210–219. doi: 10.1016/j.omtm.2020.09.005
84. Chen Y, Yang S, Yao W, Zhu H, Xu X, Meng G, Zhang W. Prostacyclin analogue beraprost inhibits cardiac fibroblast proliferation depending on prostacyclin receptor activation through a TGF β-Smad signal pathway. *PLoS One*. 2014;9:e98483. doi: 10.1371/journal.pone.0098483
85. Catalán M, Aránguiz P, Boza P, Olmedo I, Humeres C, Vivar R, Anfossi R, Ayala P, Espinoza C, Lavandero S, et al. TGF-β1 induced up-regulation of B1 kinin receptor promotes antifibrotic activity in rat cardiac myofibroblasts. *Mol Biol Rep*. 2019;46:5197–5207. doi: 10.1007/s11033-019-04977-3
86. Kisch-Wedel H, Kemming G, Meisner F, Flondor M, Kuebler WM, Bruhn S, Koehler C, Zwissler B. The prostaglandins epoprostenol and iloprost increase left ventricular contractility in vivo. *Intensive Care Med*. 2003;29:1574–1583. doi: 10.1007/s00134-003-1891-z
87. Kisch-Wedel H, Kemming G, Meisner F, Flondor M, Bruhn S, Koehler C, Messmer K, Zwissler B. Effect of prostaglandin I2 analogues on left ventricular diastolic function in vivo. *Eur J Pharmacol*. 2005;517:208–216. doi: 10.1016/j.ejphar.2005.05.017
88. Huang CY, Lee JK, Chen ZW, Cheng JF, Chen SY, Lin LY, Wu CK. Inhaled prostacyclin on exercise echocardiographic cardiac function in preserved ejection fraction heart failure. *Med Sci Sports Exerc*. 2020;52:269–277. doi: 10.1249/MSS.0000000000002145
89. FitzGerald GA, Smith B, Pedersen AK, Brash AR. Increased prostacyclin biosynthesis in patients with severe atherosclerosis and platelet activation. *N Engl J Med*. 1984;310:1065–1068. doi: 10.1056/NEJM198404263101701
90. Kobayashi T, Tahara Y, Matsumoto M, Iguchi M, Sano H, Murayama T, Arai H, Oida H, Yurugi-Kobayashi T, Yamashita JK, et al. Roles of thromboxane A(2) and prostacyclin in the development of atherosclerosis in apoE-deficient mice. *J Clin Invest*. 2004;114:784–794. doi: 10.1172/JCI21446
91. Cheng Y, Austin SC, Rocca B, Koller BH, Coffman TM, Grosser T, Lawson JA, FitzGerald GA. Role of prostacyclin in the cardiovascular response to thromboxane A2. *Science*. 2002;296:539–541. doi: 10.1126/science.1068711
92. Rudic RD, Brinster D, Cheng Y, Fries S, Song W-l, Austin S, Coffman TM, Fitzgerald GA. COX-2-derived prostacyclin modulates vascular remodeling. *Circ Res*. 2005;96:1240–1247. doi: 10.1161/01.RES.0000170888.11669.28
93. Todaka T, Yokoyama C, Yanamoto H, Hashimoto N, Nagata I, Tsukahara T, Hara S, Hatae T, Morishita R, Aoki M, et al. Gene transfer of human prostacyclin synthase prevents neointimal formation after carotid balloon injury in rats. *Stroke*. 1990;30:419–426. doi: 10.1161/01.str.30.2.419

94. Kouchi Y, Esato K, O-Hara M, Zempo N. Effect of prostaglandin I2 analogue TRK-100 on the suppression of intimal fibrous proliferation. *J Vasc Surg*. 1992;16:232–238.
95. Wikström K, Kavanagh DJ, Reid HM, Kinsella BT. Differential regulation of RhoA-mediated signaling by the TPalpha and TPbeta isoforms of the human thromboxane A2 receptor: independent modulation of TPalpha signaling by prostacyclin and nitric oxide. *Cell Signal*. 2008;20:1497–1512. doi: 10.1016/j.cellsig.2008.04.006
96. Li Z, Luo W, Fang S, Chen X, Lin T, Zhou S, Zhang L, Yang W, Li Z, Ye J, et al. Prostacyclin facilitates vascular smooth muscle cell phenotypic transformation via activating TP receptors when IP receptors are deficient. *Acta Physiol (Oxf)*. 2021;231:e13555. doi: 10.1111/apha.13555
97. Murata T, Ushikubi F, Matsuoka T, Hirata M, Yamasaki A, Sugimoto Y, Ichikawa A, Aze Y, Tanaka T, Yoshida N, et al. Altered pain perception and inflammatory response in mice lacking prostacyclin receptor. *Nature*. 1997;388:678–682. doi: 10.1038/41780
98. Watanabe H, Katoh T, Eiro M, Iwamoto M, Ushikubi F, Narumiya S, Watanabe T. Effects of salt loading on blood pressure in mice lacking the prostanoid receptor gene. *Circ J*. 2005;69:124–126. doi: 10.1253/circj.69.124
99. D'Agostino I, Tacconelli S, Bruno A, Contursi A, Mucci L, Hu X, Xie Y, Chakraborty R, Jain K, Sacco A, et al. Low-dose aspirin prevents hypertension and cardiac fibrosis when thromboxane A2 is unrestrained. *Pharmacol Res*. 2021;170:105744. doi: 10.1016/j.phrs.2021.105744
100. Tang SY, Meng H, Anderson ST, Sarantopoulou D, Ghosh S, Lahens NF, Theken KN, Ricciotti E, Hennessy EJ, Tu V, et al. Sex-dependent compensatory mechanisms preserve blood pressure homeostasis in prostacyclin receptor-deficient mice. *J Clin Invest*. 2021;131:e136310. doi: 10.1172/JCI136310
101. Cheng Y, Vanhoutte PM, Leung SWS. Apolipoprotein E favours the blunting by high-fat diet of prostacyclin receptor activation in the mouse aorta. *Br J Pharmacol*. 2018;175:3453–3469. doi: 10.1111/bph.14386
102. Nakayama T, Hironaga T, Ishima H, Maruyama T, Masubuchi Y, Kokubun S. The prostacyclin analogue beraprost sodium prevents development of arterial stiffness in elderly patients with cerebral infarction. *Prostaglandins Leukot Essent Fatty Acids*. 2004;70:491–494. doi: 10.1016/j.plefa.2003.10.004
103. Audoly LP, Rocca B, Fabre JE, Koller BH, Thomas D, Loeb AL, Coffman TM, FitzGerald GA. Cardiovascular responses to the isoprostanes iPF(2alpha)-III and iPE(2)-III are mediated via the thromboxane A(2) receptor in vivo. *Circulation*. 2000;101:2833–2840. doi: 10.1161/01.cir.101.24.2833
104. Capra V, Bäck M, Angiolillo DJ, Cattaneo M, Sakariassen KS. Impact of vascular thromboxane prostanoid receptor activation on hemostasis, thrombosis, oxidative stress, and inflammation. *J Thromb Haemost*. 2014;12:126–137. doi: 10.1111/jth.12472
105. Mazaleuskaya LL, Ricciotti E. Druggable prostanoid pathway. *Adv Exp Med Biol*. 2020;1274:29–54. doi: 10.1007/978-3-030-50621-6_3
106. Yi X, Lin J, Luo H, Wang C, Liu Y. Genetic variants of PTGS2, TXA2R and TXAS1 are associated with carotid plaque vulnerability, platelet activation and TXA2 levels in ischemic stroke patients. *PLoS One*. 2017;12:e0180704. doi: 10.1371/journal.pone.0180704
107. Gleim S, Stitham J, Tang WH, Li H, Douville K, Chelikani P, Rade JJ, Martin KA, Hwa J. Human thromboxane A2 receptor genetic variants: in silico, in vitro and "in platelet" analysis. *PLoS One*. 2013;8:e67314. doi: 10.1371/journal.pone.0067314
108. Nossent AY, Hansen JL, Doggen C, Quax PH, Sheikh SP, Rosendaal FR. SNPs in microRNA binding sites in 3'-UTRs of RAAS genes influence arterial blood pressure and risk of myocardial infarction. *Am J Hypertens*. 2011;24:999–1006. doi: 10.1038/ajh.2011.92
109. Nichols WW, Mehta J, Wargovich TJ, Franzini D, Lawson D. Reduced myocardial neutrophil accumulation and infarct size following thromboxane synthetase inhibitor or receptor antagonist. *Angiology*. 1989;40:209–221. doi: 10.1177/000331978904000309
110. Chiang CY, Chien CY, Qiou WY, Chang C, Yu IS, Chang PY, Chien CT. Genetic depletion of thromboxane A2/thromboxane-prostanoid receptor signalling prevents microvascular dysfunction in ischaemia/reperfusion injury. *Thromb Haemost*. 2018;118:1982–1996. doi: 10.1055/s-0038-1672206
111. Hirata Y, Shimabukuro M, Uematsu E, Soeki T, Yamada H, Sakai Y, Nakayama M, Matsumoto K, Igarashi T, Sata M. A synthetic prostacyclin agonist with thromboxane synthase inhibitory activity, ONO-1301, protects myocardium from ischemia/reperfusion injury. *Eur J Pharmacol*. 2012;674:352–358. doi: 10.1016/j.ejphar.2011.10.038
112. Takayama K, Yuhki K, Ono K, Fujino T, Hara A, Yamada T, Kuriyama S, Karibe H, Okada Y, Takahata O, et al. Thromboxane A2 and prostaglandin F2alpha mediate inflammatory tachycardia. *Nat Med*. 2005;11:562–566. doi: 10.1038/nm1231
113. Butenas ALE, Rollins KS, Williams AC, Parr SK, Hammond ST, Ade CJ, Hageman KS, Musch TI, Copp SW. Thromboxane A2 receptors contribute to the exaggerated exercise pressor reflex in male rats with heart failure. *Physiol Rep*. 2021;9:e15052. doi: 10.14814/phy2.15052
114. West JD, Voss BM, Pavliv L, de Caestecker M, Hemnes AR, Carrier EJ. Antagonism of the thromboxane-prostanoid receptor is cardioprotective against right ventricular pressure overload. *Pulm Circ*. 2016;6:211–223. doi: 10.1086/686140
115. Mulvaney EP, Renzo F, Adão R, Dupre E, Bialesova L, Salvatore V, Reid HM, Conceição G, Grynblat J, Llucià-Valldeperas A, et al. The thromboxane receptor antagonist NTP42 promotes beneficial adaptation and preserves cardiac function in experimental models of right heart overload. *Front Cardiovasc Med*. 2022;9:1063967. doi: 10.3389/fcvm.2022.1063967
116. Wacker MJ, Best SR, Kosloski LM, Stachura CJ, Smoot RL, Porter CB, Orr JA. Thromboxane A2-induced arrhythmias in the anesthetized rabbit. *Am J Physiol Heart Circ Physiol*. 2006;290:H1353–H1361. doi: 10.1152/ajpheart.00930.2005
117. Hariri E, Kakouros N, Bunsick DA, Russell SD, Mudd JO, Laws K, Lake MW, Rade JJ. Nonplatelet thromboxane generation is associated with impaired cardiovascular performance and mortality in heart failure. *Am J Physiol Heart Circ Physiol*. 2022;323:H248–H255. doi: 10.1152/ajpheart.00212.2022
118. . Wang N, Vendrov KC, Simmons BP, Schuck RN, Stouffer GA, Lee CR. Urinary 11-dehydro-thromboxane B2 levels are associated with vascular inflammation and prognosis in atherosclerotic cardiovascular disease. *Prostaglandins Other Lipid Mediat*. 2018;134:24–31. doi: 10.1016/j.prostaglandins.2017.11.003
119. Huang SW, Lien JC, Kuo SC, Huang TF. Inhibitory effects of an orally active thromboxane A2 receptor antagonist, nstpbp5185, on atherosclerosis in ApoE-deficient mice. *Thromb Haemost*. 2018;118:401–414. doi: 10.1160/TH17-07-0519
120. Egan KM, Wang M, Fries S, Lucitt MB, Zukas AM, Puré E, Lawson JA, FitzGerald GA, Cyclooxygenases, thromboxane, atherosclerosis: plaque destabilization by cyclooxygenase-2 inhibition combined with thromboxane receptor antagonism. *Circulation*. 2005;111:334–342. doi: 10.1161/01.CIR.0000153386.95356.78
121. Zuccollo A, Shi C, Mastroianni R, Maitland-Toolan KA, Weisbrod RM, Zang M, Xu S, Jiang B, Oliver-Krasinski JM, Cayatte AJ, et al. The thromboxane A2 receptor antagonist S18886 prevents enhanced atherogenesis caused by diabetes mellitus. *Circulation*. 2005;112:3001–3008. doi: 10.1161/CIRCULATIONAHA.105.581892
122. Cyrus T, Yao Y, Ding T, Dogne JM, Pratico D. A novel thromboxane receptor antagonist and synthase inhibitor, BM-573, reduces development and progression of atherosclerosis in LDL receptor deficient mice. *Eur J Pharmacol*. 2007;561:105–111. doi: 10.1016/j.ejphar.2006.12.024
123. Cherdon C, Rolin S, Hanson J, Ooms A, de Leval L, Drion P, Michiels C, Pirotte B, Masereel B, Sakalihassan N, et al. BM-573 inhibits the development of early atherosclerotic lesions in Apo E deficient mice by blocking TP receptors and thromboxane synthase. *Prostaglandins Other Lipid Mediat*. 2011;94:124–132. doi: 10.1016/j.prostaglandins.2011.03.001
124. Romero M, Leon-Gomez E, Lobysheva I, Rath G, Dogné JM, Feron O, Dessy C. Effects of BM-573 on endothelial dependent relaxation and increased blood pressure at early stages of atherosclerosis. *PLoS One*. 2016;11:e0152579. doi: 10.1371/journal.pone.0152579
125. Braun H, Hauke M, Eckenstaler R, Petermann M, Ripperger A, Kühn N, SchwedhelmE,Ludwig-KrausB,KrausFB,DubourgV,etal.TheF2-isoprostane 8-iso-PGF2α attenuates atherosclerotic lesion formation in Ldlr-deficient mice - potential role of vascular thromboxane A2 receptors. *Free Radic Biol Med*. 2022;185:36–45. doi: 10.1016/j.freeradbiomed.2022.04.010
126. Zhuge X, Arai H, Xu Y, Murayama T, Kobayashi T, Narumiya S, Kita T, Yokode M. Protection of atherogenesis in thromboxane A2 receptor-deficient mice is not associated with thromboxane A2 receptor in bone marrow-derived cells. *Biochem Biophys Res Commun*. 2006;351:865–871. doi: 10.1016/j.bbrc.2006.10.121
127. Francois H, Makhanova N, Ruiz P, Ellison J, Mao L, Rockman HA, Coffman TM. A role for the thromboxane receptor in L-NAME hypertension. *Am J Physiol Renal Physiol*. 2008;295:F1096–F1102. doi: 10.1152/ajprenal.00369.2007
128. Francois H, Athirakul K, Mao L, Rockman H, Coffman TM. Role for thromboxane receptors in angiotensin-II-induced hypertension. *Hypertension*. 2004;43:364–369. doi: 10.1161/01.HYP.0000112225.27560.24
129. Yamada T, Fujino T, Yuhki K, Hara A, Karibe H, Takahata O, Okada Y, Xiao CY, Takayama K, Kuriyama S, et al. Thromboxane A2 regulates vascular tone via its inhibitory effect on the expression of

inducible nitric oxide synthase. *Circulation*. 2003;108:2381–2386. doi: 10.1161/01.CIR.0000093194.21109.EC
130. Sparks MA, Makhanova NA, Griffiths RC, Snouwaert JN, Koller BH, Coffman TM. Thromboxane receptors in smooth muscle promote hypertension, vascular remodeling, and sudden death. *Hypertension*. 2013;61:166–173. doi: 10.1161/HYPERTENSIONAHA.112.193250
131. Gelosa P, Sevin G, Pignieri A, Budelli S, Castiglioni L, Blanc-Guillemaud V, Lerond L, Tremoli E, Sironi L. Terutroban, a thromboxane/prostaglandin endoperoxide receptor antagonist, prevents hypertensive vascular hypertrophy and fibrosis. *Am J Physiol Heart Circ Physiol*. 2011;300:H762–H768. doi: 10.1152/ajpheart.00880.2010
132. Hegener HH, Diehl KA, Kurth T, Gaziano JM, Ridker PM, Zee RY. Polymorphisms of prostaglandin-endoperoxide synthase 2 gene, and prostaglandin-E receptor 2 gene, C-reactive protein concentrations and risk of atherothrombosis: a nested case-control approach. *J Thromb Haemost*. 2006;4:1718–1722. doi: 10.1111/j.1538-7836.2006.02054.x
133. Sato M, Nakayama T, Soma M, Aoi N, Kosuge K, Haketa A, Izumi Y, Matsumoto K, Sato N, Kokubun S. Association between prostaglandin E2 receptor gene and essential hypertension. *Prostaglandins Leukot Essent Fatty Acids*. 2007;77:15–20. doi: 10.1016/j.plefa.2007.04.004
134. Szczeklik W, Sanak M, Rostoff P, Piwowarska W, Jakiela B, Szczeklik A. Common polymorphisms of cyclooxygenase-2 and prostaglandin E2 receptor and increased risk for acute coronary syndrome in coronary artery disease. *Thromb Haemost*. 2008;100:893–898.
135. Zhu L, Xu C, Huo X, Hao H, Wan Q, Chen H, Zhang X, Breyer RM, Huang Y, Cao X, et al. The cyclooxygenase-1/mPGES-1/endothelial prostaglandin EP4 receptor pathway constrains myocardial ischemia-reperfusion injury. *Nat Commun*. 2019;10:1888. doi: 10.1038/s41467-019-09492-4
136. Degousee N, Fazel S, Angoulvant D, Stefanski E, Pawelzik SC, Korotkova M, Arab S, Liu P, Lindsay TF, Zhuo S, et al. Microsomal prostaglandin E2 synthase-1 deletion leads to adverse left ventricular remodeling after myocardial infarction. *Circulation*. 2008;117:1701–1710. doi: 10.1161/CIRCULATIONAHA.107.749739
137. Degousee N, Simpson J, Fazel S, Scholich K, Angoulvant D, Angioni C, Schmidt H, Korotkova M, Stefanski E, Wang XH, et al. Lack of microsomal prostaglandin E2 synthase-1 in bone marrow-derived myeloid cells impairs left ventricular function and increases mortality after acute myocardial infarction. *Circulation*. 2012;125:2904–2913. doi: 10.1161/CIRCULATIONAHA.112.099754
138. Chen L, Yang G, Jiang T, Tang SY, Wang T, Wan Q, Wang M, FitzGerald GA. Myeloid cell mPges-1 deletion attenuates mortality without affecting remodeling after acute myocardial infarction in mice. *J Pharmacol Exp Ther*. 2019;370:18–24. doi: 10.1124/jpet.118.256057
139. Zhang Y, Steinmetz-Späh J, Idborg H, Zhu L, Li H, Rao H, Chen Z, Guo Z, Hu L, Xu C, et al. Microsomal prostaglandin E synthase-1 inhibition prevents adverse cardiac remodelling after myocardial infarction in mice. *Br J Pharmacol*. 2023;180:1981–1998. doi: 10.1111/bph.16061
140. Wu D, Mennerich D, Arndt K, Sugiyama K, Ozaki N, Schwarz K, Wei J, Wu H, Bishopric NH, Doods H. The effects of microsomal prostaglandin E synthase-1 deletion in acute cardiac ischemia in mice. *Prostaglandins Leukot Essent Fatty Acids*. 2009;81:31–33. doi: 10.1016/j.plefa.2009.05.019
141. Wu JMF, Cheng YY, Tang TWH, Shih C, Chen JH, Hsieh PCH. Prostaglandin E2 receptor 2 modulates macrophage activity for cardiac repair. *J Am Heart Assoc*. 2018;7:e009216. doi: 10.1161/JAHA.118.009216
142. Tang J, Shen Y, Chen G, Wan Q, Wang K, Zhang J, Qin J, Liu G, Zuo S, Tao B, et al. Activation of E-prostanoid 3 receptor in macrophages facilitates cardiac healing after myocardial infarction. *Nat Commun*. 2017;8:14656. doi: 10.1038/ncomms14656
143. Maxwell DL, Bryson TD, Taube D, Xu J, Peterson E, Harding P. Deleterious effects of cardiomyocyte-specific prostaglandin E2 EP3 receptor overexpression on cardiac function after myocardial infarction. *Life Sci*. 2023;313:121277. doi: 10.1016/j.lfs.2022.121277
144. Meyer-Kirchrath J, Martin M, Schooss C, Jacoby C, Flögel U, Marzoll A, Fischer JW, Schrader J, Schrör K, Hohlfeld T. Overexpression of prostaglandin EP3 receptors activates calcineurin and promotes hypertrophy in the murine heart. *Cardiovasc Res*. 2009;81:310–318. doi: 10.1093/cvr/cvn312
145. Zacharowski K, Olbrich A, Piper J, Hafner G, Kondo K, Thiemermann C. Selective activation of the prostanoid EP(3) receptor reduces myocardial infarct size in rodents. *Arterioscler Thromb Vasc Biol*. 1999;19:2141–2147. doi: 10.1161/01.atv.19.9.2141
146. Hohlfeld T, Meyer-Kirchrath J, Vogel YC, Schrör K. Reduction of infarct size by selective stimulation of prostaglandin EP(3)receptors in the reperfused ischemic pig heart. *J Mol Cell Cardiol*. 2000;32:285–296. doi: 10.1006/jmcc.1999.1072
147. Xiao CY, Yuhki K, Hara A, Fujino T, Kuriyama S, Yamada T, Takayama K, Takahata O, Karibe H, Taniguchi T, et al. Prostaglandin E2 protects the heart from ischemia-reperfusion injury via its receptor subtype EP4. *Circulation*. 2004;109:2462–2468. doi: 10.1161/01.CIR.0000128046.54681.97
148. Kanno T, Nakagawa N, Aonuma T, Kawabe JI, Yuhki KI, Takehara N, Hasebe N, Ushikubi F. Prostaglandin E2 mediates the late phase of ischemic preconditioning in the heart via its receptor subtype EP4. *Heart Vessels*. 2023;38:606–613. doi: 10.1007/s00380-022-02219-4
149. Hishikari K, Suzuki J, Ogawa M, Isobe K, Takahashi T, Onishi M, Takayama K, Isobe M. Pharmacological activation of the prostaglandin E2 receptor EP4 improves cardiac function after myocardial ischaemia/reperfusion injury. *Cardiovasc Res*. 2009;81:123–132. doi: 10.1093/cvr/cvn254
150. Qian JY, Harding P, Liu Y, Shesely E, Yang XP, LaPointe MC. Reduced cardiac remodeling and function in cardiac-specific EP4 receptor knockout mice with myocardial infarction. *Hypertension*. 2008;51:560–566. doi: 10.1161/HYPERTENSIONAHA.107.102590
151. Bryson TD, Gu X, Khalil RM, Khan S, Zhu L, Xu J, Peterson E, Yang XP, Harding P. Overexpression of prostaglandin E2 EP4 receptor improves cardiac function after myocardial infarction. *J Mol Cell Cardiol*. 2018;118:1–12. doi: 10.1016/j.yjmcc.2018.03.005
152. Fu J, Li L, Chen L, Su C, Feng X, Huang K, Zhang L, Yang X, Fu Q. PGE2 protects against heart failure through inhibiting TGF-β1 synthesis in cardiomyocytes and crosstalk between TGF-β1 and GRK2. *J Mol Cell Cardiol*. 2022;172:63–77. doi: 10.1016/j.yjmcc.2022.07.012
153. Harding P, Yang XP, He Q, Lapointe MC. Lack of microsomal prostaglandin E synthase-1 reduces cardiac function following angiotensin II infusion. *Am J Physiol Heart Circ Physiol*. 2011;300:H1053–H1061. doi: 10.1152/ajpheart.00772.2010
154. Ji S, Guo R, Wang J, Qian L, Liu M, Xu H, Zhang J, Guan Y, Yang G, Chen L. Microsomal prostaglandin E2 synthase-1 deletion attenuates isoproterenol-induced myocardial fibrosis in mice. *J Pharmacol Exp Ther*. 2020;375:40–48. doi: 10.1124/jpet.120.000023
155. Ballesteros-Martínez C, Rodrigues-Díez R, Beltrán LM, Moreno-Carriles R, Martínez-Martínez E, González-Amor M, Martínez-González J, Rodríguez C, Cachofeiro V, Salaices M, et al. Microsomal prostaglandin E synthase-1 is involved in the metabolic and cardiovascular alterations associated with obesity. *Br J Pharmacol*. 2022;179:2733–2753. doi: 10.1111/bph.15776
156. Liu S, Ji Y, Yao J, Zhao X, Xu H, Guan Y, Breyer RM, Sheng H, Zhu J. Knockout of the prostaglandin E2 receptor subtype 3 promotes eccentric cardiac hypertrophy and fibrosis in mice. *J Cardiovasc Pharmacol Ther*. 2017;22:71–82. doi: 10.1177/1074248416642520
157. Ying F, Liu H, Ching Tang EH, Lakhani I, Liu N, Xia Z, Liu S. Prostaglandin E receptor subtype 4 protects against diabetic cardiomyopathy by modulating cardiac fatty acid metabolism via FOXO1/CD36 signalling. *Biochem Biophys Res Commun*. 2021;548:196–203. doi: 10.1016/j.bbrc.2021.01.038
158. Harding P, Yang XP, Yang J, Shesely E, He Q, LaPointe MC. Gene expression profiling of dilated cardiomyopathy in older male EP4 knockout mice. *Am J Physiol Heart Circ Physiol*. 2010;298:H623–H632. doi: 10.1152/ajpheart.00746.2009
159. Wang Q, Oka T, Yamagami K, Lee JK, Akazawa H, Naito AT, Yasui T, Ishizu T, Nakaoka Y, Sakata Y, et al. An EP4 receptor agonist inhibits cardiac fibrosis through activation of PKA signaling in hypertrophied heart. *Int Heart J*. 2017;58:107–114. doi: 10.1536/ihj.16-200
160. Takakuma A, Nishii M, Valaperti A, Hiraga H, Saji R, Sakai K, Matsumura R, Miyata Y, Oba N, Nunose F, et al. Prostaglandin-E2 receptor-4 stimulant rescues cardiac malfunction during myocarditis and protects the heart from adverse ventricular remodeling after myocarditis. *Sci Rep*. 2021;11:20961. doi: 10.1038/s41598-021-99930-5
161. Ngoc PB, Suzuki J, Ogawa M, Hishikari K, Takayama K, Hirata Y, Nagai R, Isobe M. The anti-inflammatory mechanism of prostaglandin E2 receptor 4 activation in rat experimental autoimmune myocarditis. *J Cardiovasc Pharmacol*. 2011;57:365–372. doi: 10.1097/FJC.0b013e31820b7be1
162. Gu X, Xu J, Zhu L, Bryson T, Yang XP, Peterson E, Harding P. Prostaglandin E2 reduces cardiac contractility via EP3 receptor. *Circ Heart Fail*. 2016;9:10.1161. doi: 10.1161/CIRCHEARTFAILURE.116.003291
163. Hsueh YC, Wu JM, Yu CK, Wu KK, Hsieh PC. Prostaglandin E_2 promotes post-infarction cardiomyocyte replenishment by endogenous stem cells. *EMBO Mol Med*. 2014;6:496–503. doi: 10.1002/emmm.201303687
164. Gomez I, Foudi N, Longrois D, Norel X. The role of prostaglandin E2 in human vascular inflammation. *Prostaglandins Leukot Essent Fatty Acids*. 2013;89:55–63. doi: 10.1016/j.plefa.2013.04.004
165. Cipollone F, Prontera C, Pini B, Marini M, Fazia M, De Cesare D, Iezzi A, Ucchino S, Boccoli G, Saba V, et al. Overexpression of functionally coupled

cyclooxygenase-2 and prostaglandin E synthase in symptomatic atherosclerotic plaques as a basis of prostaglandin E(2)-dependent plaque instability. *Circulation*. 2001;104:921–927. doi: 10.1161/hc3401.093152
166. Gómez-Hernández A, Martín-Ventura JL, Sánchez-Galán E, Vidal C, Ortego M, Blanco-Colio LM, Ortega L, Tuñón J, Egido J. Overexpression of COX-2, prostaglandin E synthase-1 and prostaglandin E receptors in blood mononuclear cells and plaque of patients with carotid atherosclerosis: regulation by nuclear factor-kappaB. *Atherosclerosis*. 2006;187:139–149. doi: 10.1016/j.atherosclerosis.2005.08.035
167. Cipollone F, Fazia ML, Iezzi A, Cuccurullo C, De Cesare D, Ucchino S, Spigonardo F, Marchetti A, Buttitta F, Paloscia L, et al. Association between prostaglandin E receptor subtype EP4 overexpression and unstable phenotype in atherosclerotic plaques in human. *Arterioscler Thromb Vasc Biol*. 2005;25:1925–1931. doi: 10.1161/01.ATV.0000177814.41505.41
168. Wang M, Zukas AM, Hui Y, Ricciotti E, Pure E, FitzGerald GA. Deletion of microsomal prostaglandin E synthase-1 augments prostacyclin and retards atherogenesis. *Proc Natl Acad Sci U S A*. 2006;103:14507–14512. doi: 10.1073/pnas.0606586103
169. Chen L, Yang G, Monslow J, Todd L, Cormode DP, Tang J, Grant GR, DeLong JH, Tang SY, Lawson JA, et al. Myeloid cell microsomal prostaglandin E synthase-1 fosters atherogenesis in mice. *Proc Natl Acad Sci U S A*. 2014;111:6828–6833. doi: 10.1073/pnas.1401797111
170. Tang SY, Monslow J, Grant G R, Todd L, Pawelzik SC, Chen L, Lawson J, Puré E, FitzGerald GA. Cardiovascular consequences of prostanoid I receptor deletion in microsomal prostaglandin E synthase-1-deficient hyperlipidemic mice. *Circulation*. 2016;134:328–338. doi: 10.1161/CIRCULATIONAHA.116.022308
171. Gross S, Tilly P, Hentsch D, Vonesch JL, Fabre JE. Vascular wall-produced prostaglandin E2 exacerbates arterial thrombosis and atherothrombosis through platelet EP3 receptors. *J Exp Med*. 2007;204:311–320. doi: 10.1084/jem.20061617
172. Babaev VR, Chew JD, Ding L, Davis S, Breyer MD, Breyer RM, Oates JA, Fazio S, Linton MF. Macrophages EP4 deficiency increases apoptosis and suppresses early atherosclerosis. *Cell Metab*. 2008;8:492–501. doi: 10.1016/j.cmet.2008.09.005
173. Vallerie SN, Kramer F, Barnhart S, Kanter JE, Breyer RM, Andreasson KI, Bornfeldt KE. Myeloid cell prostaglandin E2 receptor EP4 modulates cytokine production but not atherogenesis in a mouse model of type 1 diabetes. *PLoS One*. 2016;11:e0158316. doi: 10.1371/journal.pone.0158316
174. Tang EH, Shimizu K, Christen T, Rocha VZ, Shvartz E, Tesmenitsky Y, Sukhova G, Shi GP, Libby P. Lack of EP4 receptors on bone marrow-derived cells enhances inflammation in atherosclerotic lesions. *Cardiovasc Res*. 2011;81:234–243. doi: 10.1093/cvr/cvq262
175. Wang M, Ihida-Stansbury K, Kothapalli D, Tamby MC, Yu Z, Chen L, Grant G, Cheng Y, Lawson JA, Assoian RK, et al. Microsomal prostaglandin e2 synthase-1 modulates the response to vascular injury. *Circulation*. 2011;123:631–639. doi: 10.1161/CIRCULATIONAHA.110.973685
176. Chen L, Yang G, Xu X, Grant G, Lawson JA, Bohlooly-Y M, FitzGerald GA. Cell selective cardiovascular biology of microsomal prostaglandin E synthase-1. *Circulation*. 2013;127:233–243. doi: 10.1161/CIRCULATIONAHA.112.119479
177. Zhang J, Zou F, Tang J, Zhang Q, Gong Y, Wang Q, Shen Y, Xiong L, Breyer RM, Lazarus M, et al. Cyclooxygenase-2-derived prostaglandin E_2 promotes injury-induced vascular neointimal hyperplasia through the E-prostanoid 3 receptor. *Circ Res*. 2013;113:104–114. doi: 10.1161/CIRCRESAHA.113.301033
178. Xu H, Fang B, Bao C, Mao X, Zhu C, Ye L, Liu Q, Li Y, Du C, Qi H, et al. The Prostaglandin E2 receptor EP4 promotes vascular neointimal hyperplasia through translational control of tenascin C via the cAPM/PKA/mTORC1/rpS6 pathway. *Cells*. 2022;11:2720. doi: 10.3390/cells11172720
179. Hao H, Hu S, Wan Q, Xu C, Chen H, Zhu L, Xu Z, Meng J, Breyer RM, Li N, et al. Protective role of mPGES-1 (microsomal prostaglandin E synthase-1)-derived PGE2 (prostaglandin E2) and the endothelial EP4 (prostaglandin E receptor) in vascular responses to injury. *Arterioscler Thromb Vasc Biol*. 2018;38:1115–1124. doi: 10.1161/ATVBAHA.118.310713
180. Zhu S, Xue R, Zhao P, Fan FL, Kong X, Zheng S, Han Q, Zhu Y, Wang N, Yang J, Guan Y. Targeted disruption of the prostaglandin E2 E-prostanoid 2 receptor exacerbates vascular neointimal formation in mice. *Arterioscler Thromb Vasc Biol*. 2011;31:1739–1747. doi: 10.1161/ATVBAHA.111.226142
181. Camacho M, Dilmé J, Solà-Villà D, Rodríguez C, Bellmunt S, Siguero L, Alcolea S, Romero JM, Escudero JR, Martínez-González J, et al. Microvascular COX-2/mPGES-1/EP-4 axis in human abdominal aortic aneurysm. *J Lipid Res*. 2013;54:3506–3515. doi: 10.1194/jlr.M042481
182. Yokoyama U, Ishiwata R, Jin MH, Kato Y, Suzuki O, Jin H, Ichikawa Y, Kumagaya S, Katayama Y, Fujita T, et al. Inhibition of EP4 signaling attenuates aortic aneurysm formation. *PLoS One*. 2012;7:e36724. doi: 10.1371/journal.pone.0036724
183. Wang M, Lee E, Song W, Ricciotti E, Rader DJ, Lawson JA, Pure E, FitzGerald GA. Microsomal prostaglandin E synthase-1 deletion suppresses oxidative stress and angiotensin II-induced abdominal aortic aneurysm formation. *Circulation*. 2008;117:1302–1309. doi: 10.1161/CIRCULATIONAHA.107.731398
184. Cao RY, St Amand T, Li X, Yoon SH, Wang CP, Song H, Maruyama T, Brown PM, Zelt DT, Funk CD. Prostaglandin receptor EP4 in abdominal aortic aneurysms. *Am J Pathol*. 2012;181:313–321. doi: 10.1016/j.ajpath.2012.03.016
185. Mamun A, Yokoyama U, Saito J, Ito S, Hiromi T, Umemura M, Fujita T, Yasuda S, Minami T, Goda M, et al. A selective antagonist of prostaglandin E receptor subtype 4 attenuates abdominal aortic aneurysm. *Physiol Rep*. 2018;6:e13878. doi: 10.14814/phy2.13878
186. Xu H, Du S, Fang B, Li C, Jia X, Zheng S, Wang S, Li Q, Su W, Wang N, et al. VSMC-specific EP4 deletion exacerbates angiotensin II-induced aortic dissection by increasing vascular inflammation and blood pressure. *Proc Natl Acad Sci U S A*. 2019;116:8457–8462. doi: 10.1073/pnas.1902119116
187. Tang EH, Shvartz E, Shimizu K, Rocha VZ, Zheng C, Fukuda D, Shi GP, Sukhova G, Libby P. Deletion of EP4 on bone marrow-derived cells enhances inflammation and angiotensin II-induced abdominal aortic aneurysm formation. *Arterioscler Thromb Vasc Biol*. 2011;31:261–269. doi: 10.1161/ATVBAHA.110.216580
188. Hiromi T, Yokoyama U, Kurotaki D, Mamun A, Ishiwata R, Ichikawa Y, Nishihara H, Umemura M, Fujita T, Yasuda S, et al. Excessive EP4 signaling in smooth muscle cells induces abdominal aortic aneurysm by amplifying inflammation. *Arterioscler Thromb Vasc Biol*. 2020;40:1559–1573. doi: 10.1161/ATVBAHA.120.314297
189. Jia Z, Zhang A, Zhang H, Dong Z, Yang T. Deletion of microsomal prostaglandin E synthase-1 increases sensitivity to salt loading and angiotensin II infusion. *Circ Res*. 2006;99:1243–1251. doi: 10.1161/01.RES.0000251306.40546.08
190. Facemire CS, Griffiths R, Audoly LP, Koller BH, Coffman TM. The impact of microsomal prostaglandin e synthase 1 on blood pressure is determined by genetic background. *Hypertension*. 2010;55:531–538. doi: 10.1161/HYPERTENSIONAHA.109.145631
191. Francois H, Facemire C, Kumar A, Audoly L, Koller B, Coffman T. Role of microsomal prostaglandin E synthase 1 in the kidney. *J Am Soc Nephrol*. 2007;18:1466–1475. doi: 10.1681/ASN.2006040343
192. Jia Z, Aoyagi T, Yang T. mPGES-1 protects against DOCA-salt hypertension via inhibition of oxidative stress or stimulation of NO/cGMP. *Hypertension*. 2010;55:539–546. doi: 10.1161/HYPERTENSIONAHA.109.144840
193. Cheng Y, Wang M, Yu Y, Lawson J, Funk CD, FitzGerald GA. Cyclooxygenases, microsomal prostaglandin E synthase-1, and cardiovascular function. *J Clin Invest*. 2006;116:1391–1399. doi: 10.1172/JCI27540
194. Jia Z, Guo X, Zhang H, Wang MH, Dong Z, Yang T. Microsomal prostaglandin synthase-1-derived prostaglandin E2 protects against angiotensin II-induced hypertension via inhibition of oxidative stress. *Hypertension*. 2008;52:952–959. doi: 10.1161/HYPERTENSIONAHA.108.111229
195. Zhang MZ, Yao B, Wang Y, Yang S, Wang S, Fan X, Harris RC. Inhibition of cyclooxygenase-2 in hematopoietic cells results in salt-sensitive hypertension. *J Clin Invest*. 2015;125:4281–4294. doi: 10.1172/JCI81550
196. Guan Y, Zhang Y, Wu J, Qi Z, Yang G, Dou D, Gao Y, Chen L, Zhang X, Davis LS, et al. Antihypertensive effects of selective prostaglandin E2 receptor subtype 1 targeting. *J Clin Invest*. 2007;117:2496–2505. doi: 10.1172/JCI29838
197. Stock JL, Shinjo K, Burkhardt J, Roach M, Taniguchi K, Ishikawa T, Kim HS, Flannery PJ, Coffman TM, McNeish JD, et al. The prostaglandin E2 EP1 receptor mediates pain perception and regulates blood pressure. *J Clin Invest*. 2001;107:325–331. doi: 10.1172/JCI6749
198. Bartlett CS, Boyd KL, Harris RC, Zent R, Breyer RM. EP1 disruption attenuates end-organ damage in a mouse model of hypertension. *Hypertension*. 2012;60:1184–1191. doi: 10.1161/HYPERTENSIONAHA.112.199026
199. Avendaño MS, Martínez-Revelles S, Aguado A, Simões MR, González-Amor M, Palacios R, Guillem-Llobat P, Vassallo DV, Vila L, García-Puig J, et al. Role of COX-2-derived PGE2 on vascular stiffness and function in hypertension. *Br J Pharmacol*. 2016;173:1541–1555. doi: 10.1111/bph.13457
200. Chen L, Miao Y, Zhang Y, Dou D, Liu L, Tian X, Yang G, Pu D, Zhang X, Kang J, et al. Inactivation of the E-prostanoid 3 receptor attenuates the angiotensin II pressor response via decreasing arterial contractility. *Arterioscler Thromb Vasc Biol*. 2012;32:3024–3032. doi: 10.1161/ATVBAHA.112.254052
201. Bryson TD, Pandrangi TS, Khan SZ, Xu J, Pavlov TS, Ortiz PA, Peterson E, Harding P. The deleterious role of the prostaglandin E2 EP3

receptor in angiotensin II hypertension. *Am J Physiol Heart Circ Physiol*. 2020;318:H867–H882. doi: 10.1152/ajpheart.00538.2019
202. Kennedy CR, Zhang Y, Brandon S, Guan Y, Coffee K, Funk CD, Magnuson MA, Oates JA, Breyer MD, Breyer RM. Salt-sensitive hypertension and reduced fertility in mice lacking the prostaglandin EP2 receptor. *Nat Med*. 1999;5:217–220. doi: 10.1038/5583
203. Yang T, Song C, Ralph DL, Andrews P, Sparks MA, Koller BH, McDonough AA, Coffman TM. Cell-specific actions of the prostaglandin E-prostanoid receptor 4 attenuating hypertension: a dominant role for kidney epithelial cells compared with macrophages. *J Am Heart Assoc*. 2022;11:e026581. doi: 10.1161/JAHA.122.026581
204. Xu H, Fang B, Du S, Wang S, Li Q, Jia X, Bao C, Ye L, Sui X, Qian L, et al. Endothelial cell prostaglandin E2 receptor EP4 is essential for blood pressure homeostasis. *JCI Insight*. 2020;5:e138505. doi: 10.1172/jci.insight.138505
205. Sun CJ, Li L, Li X, Zhang WY, Liu XW. Novel SNPs of WNK1 and AKR1C3 are associated with preeclampsia. *Gene*. 2018;668:27–32. doi: 10.1016/j.gene.2018.05.055
206. Xiao B, Gu SM, Li MJ, Li J, Tao B, Wang Y, Wang Y, Zuo S, Shen Y, Yu Y, et al. Rare SNP rs12731181 in the miR-590-3p target site of the prostaglandin F2alpha receptor gene confers risk for essential hypertension in the Han Chinese population. *Arterioscler Thromb Vasc Biol*. 2015;35:1687–1695. doi: 10.1161/ATVBAHA.115.305445
207. Chazov EI, Pomoinetsky VD, Geling NG, Orlova TR, Nekrasova AA, Smirnov VN. Heart adaptation to acute pressure overload: an involvement of endogenous prostaglandins. *Circ Res*. 1979;45:205–211. doi: 10.1161/01.res.45.2.205
208. Harding P, Murray DB. The contribution of prostaglandins versus prostacyclin in ventricular remodeling during heart failure. *Life Sci*. 2011;89:671–676. doi: 10.1016/j.lfs.2011.07.025
209. Liang J, Cao Y, He M, Li W, Huang G, Ma T, Li M, Huang Y, Huang X, Hu Y. AKR1C3 and its transcription factor HOXB4 are promising diagnostic biomarkers for acute myocardial infarction. *Front Cardiovasc Med*. 2021;8:694238. doi: 10.3389/fcvm.2021.694238
210. Hu Z, Liu R, Hu H, Ding X, Ji Y, Li G, Wang Y, Xie S, Liu X, Ding Z. Potential biomarkers of acute myocardial infarction based on co-expression network analysis. *Exp Ther Med*. 2022;23:162. doi: 10.3892/etm.2021.11085
211. Berg K, Wiseth R, Bjerve K, Brurok H, Gunnes S, Skarra S, Jynge P, Basu S. Oxidative stress and myocardial damage during elective percutaneous coronary interventions and coronary angiography a comparison of blood-borne isoprostane and troponin release. *Free Radic Res*. 2004;38:517–525. doi: 10.1080/10715760410001688339
212. Sugimoto Y, Hasumoto K, Namba T, Irie A, Katsuyama M, Negishi M, Kakizuka A, Narumiya S, Ichikawa A. Cloning and expression of a cDNA for mouse prostaglandin F receptor. *J Biol Chem*. 1994;269:1356–1360.
213. Pönicke K, Giessler C, Grapow M, Heinroth-Hoffmann I, Becker K, Osten B, Brodde OE. FP-receptor mediated trophic effects of prostanoids in rat ventricular cardiomyocytes. *Br J Pharmacol*. 2000;129:1723–1731. doi: 10.1038/sj.bjp.0703243
214. Jovanović N, Pavlović M, Mircevski V, Du Q, Jovanović A. An unexpected negative inotropic effect of prostaglandin F2alpha in the rat heart. *Prostaglandins Other Lipid Mediat*. 2006;80:110–119. doi: 10.1016/j.prostaglandins.2006.05.014
215. Lai J, Jin H, Yang R, Winer J, Li W, Yen R, King KL, Zeigler F, Ko A, Cheng J, et al. Prostaglandin F2 alpha induces cardiac myocyte hypertrophy in vitro and cardiac growth in vivo. *Am J Physiol*. 1996;271:H2197–H2208. doi: 10.1152/ajpheart.1996.271.6.H2197
216. Ding WY, Ti Y, Wang J, Wang ZH, Xie GL, Shang YY, Tang MX, Zhang Y, Zhang W, Zhong M. Prostaglandin F2alpha facilitates collagen synthesis in cardiac fibroblasts via an F-prostanoid receptor/protein kinase C/Rho kinase pathway independent of transforming growth factor beta1. *Int J Biochem Cell Biol*. 2012;44:1031–1039. doi: 10.1016/j.biocel.2012.03.013
217. Ding WY, Liu L, Wang ZH, Tang MX, Ti Y, Han L, Zhang L, Zhang Y, Zhong M, Zhang W. FP-receptor gene silencing ameliorates myocardial fibrosis and protects from diabetic cardiomyopathy. *J Mol Med (Berl)*. 2014;92:629–640. doi: 10.1007/s00109-013-1119-9
218. Qian H, Luo N, Chi Y. Aging-shifted prostaglandin profile in endothelium as a factor in cardiovascular disorders. *J Aging Res*. 2012;2012:121390. doi: 10.1155/2012/121390
219. Hu BA, Sai WW, Yuan J, Lan HT, Qi J, Wang D, Zhang W, Wang ZH, Zhong M, Shang YY. PGF2α-FP receptor ameliorates senescence of VSMCs in vascular remodeling by Src/PAI-1 signal pathway. *Oxid Med Cell Longev*. 2022;2022:2908261. doi: 10.1155/2022/2908261
220. Yu Y, Lucitt MB, Stubbe J, Cheng Y, Friis UG, Hansen PB, Jensen BL, Smyth EM, FitzGerald GA. Prostaglandin F2alpha elevates blood pressure and promotes atherosclerosis. *Proc Natl Acad Sci USA*. 2009;106:7985–7990. doi: 10.1073/pnas.0811834106
221. Goupil E, Fillion D, Clément S, Luo X, Devost D, Sleno R, Pétrin D, Saragovi HU, Thorin E, Laporte SA, et al. Angiotensin II type I and prostaglandin F2α receptors cooperatively modulate signaling in vascular smooth muscle cells. *J Biol Chem*. 2015;290:3137–3148. doi: 10.1074/jbc.M114.631119
222. Li Y, Han L, Ding WY, Ti Y, Li YH, Tang MX, Wang ZH, Zhang Y, Zhang W, Zhong M. Prostaglandin F2α receptor silencing attenuates vascular remodeling in rats with type 2 diabetes. *Exp Mol Pathol*. 2015;99:517–523. doi: 10.1016/j.yexmp.2015.09.011
223. Herlong JL, Scott TR. Positioning prostanoids of the D and J series in the immunopathogenic scheme. *Immunol Lett*. 2006;102:121–131. doi: 10.1016/j.imlet.2005.10.004
224. Islam MA, Khairnar R, Fleishman J, Thompson K, Kumar S. Lipocalin-type prostaglandin D2 synthase protein- a central player in metabolism. *Pharm Res*. 2022;39:2951–2963. doi: 10.1007/s11095-022-03329-4
225. Miwa Y, Takiuchi S, Kamide K, Yoshii M, Horio T, Tanaka C, Banno M, Miyata T, Sasaguri T, Kawano Y. Identification of gene polymorphism in lipocalin-type prostaglandin D synthase and its association with carotid atherosclerosis in Japanese hypertensive patients. *Biochem Biophys Res Commun*. 2004;322:428–433. doi: 10.1016/j.bbrc.2004.07.143
226. Meng H, Sengupta A, Ricciotti E, Mrčela A, Mathew D, Mazaleuskaya LL, Ghosh S, Brooks TG, Turner AP, Schanoski AS, et al. Deep phenotyping of the lipidomic response in COVID and non-COVID sepsis. *Clin Transl Med*. 2023;13:e1440. doi: 10.1101/2023.06.02.543298
227. Wong LR, Zheng J, Wilhelmsen K, Li K, Ortiz ME, Schnicker NJ, Thurman A, Pezzulo AA, Szachowicz PJ, Li P, et al. Eicosanoid signalling blockade protects middle-aged mice from severe COVID-19. *Nature*. 2022;605:146–151. doi: 10.1038/s41586-022-04630-3
228. Zhao Q, Wu K, Li N, Li Z, Jin F. Identification of potentially relevant genes for myocardial infarction using RNA sequencing data analysis. *Exp Ther Med*. 2018;15:1456–1464. doi: 10.3892/etm.2017.5580
229. Inoue T, Eguchi Y, Matsumoto T, Kijima Y, Kato Y, Ozaki Y, Waseda K, Oda H, Seiki K, Node K, et al. Lipocalin-type prostaglandin D synthase is a powerful biomarker for severity of stable coronary artery disease. *Atherosclerosis*. 2008;201:385–391. doi: 10.1016/j.atherosclerosis.2008.03.010
230. Inoue T, Takayanagi K, Morooka S, Uehara Y, Oda H, Seiki K, Nakajima H, Urade Y. Serum prostaglandin D synthase level after coronary angioplasty may predict occurrence of restenosis. *Thromb Haemost*. 2001;85:165–170.
231. Han F, Takeda K, Ishikawa K, Ono M, Date F, Yokoyama S, Furuyama K, Shinozawa Y, Urade Y, Shibahara S. Induction of lipocalin-type prostaglandin D synthase in mouse heart under hypoxemia. *Biochem Biophys Res Commun*. 2009;385:449–453. doi: 10.1016/j.bbrc.2009.05.092
232. Qiu H, Liu JY, Wei D, Li N, Yamoah EN, Hammock BD, Chiamvimonvat N. Cardiac-generated prostanoids mediate cardiac myocyte apoptosis after myocardial ischaemia. *Cardiovasc Res*. 2012;95:336–345. doi: 10.1093/cvr/cvs191
233. Tokudome S, Sano M, Shinmura K, Matsuhashi T, Morizane S, Moriyama H, Tamaki K, Hayashida K, Nakanishi H, Yoshikawa N, et al. Glucocorticoid protects rodent hearts from ischemia/reperfusion injury by activating lipocalin-type prostaglandin D synthase-derived PGD2 biosynthesis. *J Clin Invest*. 2009;119:1477–1488. doi: 10.1172/JCI37413
234. Katsumata Y, Shinmura K, Sugiura Y, Tohyama S, Matsuhashi T, Ito H, Yan X, Ito K, Yuasa S, Ieda M, et al. Endogenous prostaglandin D2 and its metabolites protect the heart against ischemia-reperfusion injury by activating Nrf2. *Hypertension*. 2014;63:80–87. doi: 10.1161/HYPERTENSIONAHA.113.01639
235. Kong D, Shen Y, Liu G, Zuo S, Ji Y, Lu A, Nakamura M, Lazarus M, Stratakis CA, Breyer RM, et al. PKA regulatory IIα subunit is essential for PGD2-mediated resolution of inflammation. *J Exp Med*. 2016;213:2209–2226. doi: 10.1084/jem.20160459
236. Zuo S, Kong D, Wang C, Liu J, Wang Y, Wan Q, Yan S, Zhang J, Tang J, Zhang Q, et al. CRTH2 promotes endoplasmic reticulum stress-induced cardiomyocyte apoptosis through m-calpain. *EMBO Mol Med*. 2018;10:e8237. doi: 10.15252/emmm.201708237
237. Zuo S, Wang B, Liu J, Kong D, Cui H, Jia Y, Wang C, Xu X, Chen G, Wang Y, et al. ER-anchored CRTH2 antagonizes collagen biosynthesis and organ fibrosis via binding LARP6. *EMBO J*. 2021;40:e107403. doi: 10.15252/embj.2020107403
238. Hirawa N, Uehara Y, Yamakado M, Toya Y, Gomi T, Ikeda T, Eguchi Y, Takagi M, Oda H, Seiki K, et al. Lipocalin-type prostaglandin d synthase in essential hypertension. *Hypertension*. 2002;39:449–454. doi: 10.1161/hy0202.102835

239. Yalcin MU, Gurses KM, Kocyigit D, Kesikli SA, Tokgozoglu L, Guc D, Aytemir K, Ozer N. Elevated serum beta-trace protein levels are associated with the presence of atrial fibrillation in hypertension patients. *J Clin Hypertens (Greenwich)*. 2016;18:439–443. doi: 10.1111/jch.12703
240. Ragolia L, Palaia T, Hall CE, Maesaka JK, Eguchi N, Urade Y. Accelerated glucose intolerance, nephropathy, and atherosclerosis in prostaglandin D2 synthase knock-out mice. *J Biol Chem*. 2005;280:29946–29955. doi: 10.1074/jbc.M502927200
241. Tanaka R, Miwa Y, Mou K, Tomikawa M, Eguchi N, Urade Y, Takahashi-Yanaga F, Morimoto S, Wake N, Sasaguri T. Knockout of the l-pgds gene aggravates obesity and atherosclerosis in mice. *Biochem Biophys Res Commun*. 2009;378:851–856. doi: 10.1016/j.bbrc.2008.11.152
242. Song WL, Ricciotti E, Liang X, Grosser T, Grant GR, FitzGerald GA. Lipocalin-like prostaglandin D synthase but not hemopoietic prostaglandin D synthase deletion causes hypertension and accelerates thrombogenesis in mice. *J Pharmacol Exp Ther*. 2018;367:425–432. doi: 10.1124/jpet.118.250936
243. Asirvatham-Jeyaraj N, Jones AD, Burnett R, Fink GD. Brain prostaglandin D2 increases neurogenic pressor activity and mean arterial pressure in angiotensin II-salt hypertensive rats. *Hypertension*. 2019;74:1499–1506. doi: 10.1161/HYPERTENSIONAHA.119.13175
244. Song WL, Stubbe J, Ricciotti E, Alamuddin N, Ibrahim S, Crichton I, Prempeh M, Lawson JA, Wilensky RL, Rasmussen LM, et al. Niacin and biosynthesis of PGD_2 by platelet COX-1 in mice and humans. *J Clin Invest*. 2012;122:1459–1468. doi: 10.1172/JCI59262
245. Zou F, Li Y, Zhang S, Zhang J. DP1 (prostaglandin D2 receptor 1) activation protects against vascular remodeling and vascular smooth muscle cell transition to myofibroblasts in angiotensin II-induced hypertension in mice. *Hypertension*. 2022;79:1203–1215. doi: 10.1161/HYPERTENSIONAHA.121.17584
246. Weintraub NL, Blomkalns AL, Ogbi M, Horimatsu T, Benson TW, Huo Y, Fulton DJ, Agarwal G, Lee R, Winkler MA, et al. Role of prostaglandin D2 receptors in the pathogenesis of abdominal aortic aneurysm formation. *Clin Sci (Lond)*. 2022;136:309–321. doi: 10.1042/CS20220031
247. Kong D, Wan Q, Li J, Zuo S, Liu G, Liu Q, Wang C, Bai P, Duan SZ, Zhou B, et al. DP1 activation reverses age-related hypertension via NEDD4L-mediated T-bet degradation in T cells. *Circulation*. 2020;141:655–666. doi: 10.1161/CIRCULATIONAHA.119.042532