

THE INFLUENCE OF AGTR1 IN THE DEVELOPMENT OF SYSTEMIC HYPERTENSION IN ATHEROSCLEROSIS

Alexander V. Blagov^{1*}, Aleksey A. Vatlin¹, Georgii A. Orekhov², Anastasia O. Maksaeva¹, Alexander N. Orekhov²

¹Laboratory of Molecular Genetic Modeling of Inflammaging, Institute of General Pathology and Pathophysiology, 8 Baltiiskaya Street, Moscow 125315, Russia

²Institute for Atherosclerosis Research, 4-1-207, Osenniyaya Street, 121609 Moscow, Russia

*Corresponding Author: Alexander V. Blagov, al.blagov2014@gmail.com

ABSTRACT

The angiotensin II type 1 receptor (AT1R), encoded by the AGTR1 gene, is the principal effector of the renin–angiotensin–aldosterone system (RAAS) and a central node linking systemic hypertension to atherosclerosis. Through Gq/11-, Gi- and β -arrestin-dependent signaling, activation of AT1R by angiotensin II (Ang II) in vascular smooth muscle cells, endothelial cells and immune cells promotes vasoconstriction, sodium retention, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-mediated oxidative stress, inflammation, cellular proliferation and extracellular matrix remodeling. These processes simultaneously raise blood pressure and accelerate atherogenesis, so that hypertension and atherosclerosis frequently coexist and reinforce one another. The AGTR1 gene is polymorphic, and the A1166C variant (rs5186) in its 3' untranslated region has been studied intensively; it disrupts a microRNA-155 binding site, thereby increasing receptor expression, and has been associated in several meta-analyses with essential hypertension, coronary artery disease and restenosis after coronary intervention, although effect sizes are modest and population-dependent. Experimental models demonstrate that AT1R activation in the vascular wall is necessary for Ang II-induced atherosclerosis and aneurysm formation, and that receptor blockade attenuates lesion development and endothelial dysfunction. Pharmacological antagonism of AT1R with angiotensin receptor blockers (ARBs) lowers blood pressure, reduces cardiovascular events and, in several imaging studies, slows the progression of carotid intima–media thickness, in part through effects that are independent of blood pressure reduction. In this review, we integrate the molecular biology of AT1R, the functional consequences of AGTR1 polymorphism, and the experimental and clinical evidence connecting AT1R signaling to the shared pathophysiology of hypertension and atherosclerosis, and we consider the therapeutic and future research implications.

KEYWORDS: AGTR1; angiotensin II type 1 receptor; renin–angiotensin–aldosterone system; systemic hypertension; atherosclerosis; A1166C polymorphism; oxidative stress; NADPH oxidase; vascular inflammation; angiotensin receptor blockers

1. INTRODUCTION

Systemic arterial hypertension and atherosclerosis are among the most prevalent chronic disorders of the cardiovascular system and together account for the majority of myocardial infarctions, strokes and cases of heart failure worldwide. Although they are often considered separately, the two conditions share pathophysiological mechanisms, risk factors and molecular mediators, and each promotes the other: chronically elevated blood pressure accelerates atherogenesis through hemodynamic and biochemical stress on the arterial wall, while arterial stiffening and endothelial dysfunction associated with atherosclerosis contribute to the rise in blood pressure [1,2]. A key molecular link between the two is the renin–angiotensin–aldosterone system (RAAS), and in particular its dominant effector peptide, angiotensin II (Ang II), acting through the angiotensin II type 1 receptor (AT1R) [3,4]. Epidemiologically, hypertension and atherosclerotic cardiovascular disease cluster together to a degree that exceeds what would be expected from independent conditions: a large proportion of patients with coronary or carotid atherosclerosis are hypertensive, and hypertension is among the strongest modifiable predictors of atherosclerotic events. This clinical observation has long suggested a common biological substrate, and attention has increasingly focused on the RAAS as that substrate.

AT1R is a seven-transmembrane G protein-coupled receptor encoded by the AGTR1 gene on chromosome 3q24 [5,6]. It mediates virtually all of the classical cardiovascular actions of Ang II, including vasoconstriction, aldosterone secretion, renal sodium reabsorption, sympathetic activation, and the vascular remodeling, oxidative stress and inflammation that characterize both hypertensive and atherosclerotic vascular disease [3,4]. Because AT1R sits at this crossroads, variation in the AGTR1 gene, as well as changes in receptor expression and signaling, has the potential to influence susceptibility to hypertension, to atherosclerosis, and to their co-occurrence.

This review examines the role of AGTR1 and its product AT1R in the development of systemic hypertension in the context of atherosclerosis. We first summarize the structure and signaling of AT1R and the organization of the AGTR1 gene. We then review the molecular mechanisms by which AT1R activation drives hypertension and atherogenesis, the functional and epidemiological consequences of AGTR1 polymorphism, the evidence from experimental models, and the clinical implications of pharmacological AT1R blockade, before identifying remaining knowledge gaps.

2. The AGTR1 Gene and the AT1 Receptor

2.1. Gene Structure and Regulation

The human AGTR1 gene spans approximately 55 kb and comprises five exons and four introns, with the entire coding region contained within the final exon [5,6]. The 5' untranslated region is subject to complex alternative splicing, and multiple promoter and enhancer elements regulate tissue-specific expression. The 3' untranslated region (3'UTR) contains regulatory motifs, including binding sites for microRNAs, that control messenger RNA stability and translational efficiency [7,8]. Unlike rodents, which possess two distinct AT1 receptor genes (Agtr1a and Agtr1b), humans have a single AGTR1 gene; this distinction is important when interpreting data from murine models in which the Agtr1a isoform predominates in the vasculature [6].

2.2. Receptor Structure and Signaling

AT1R belongs to the class A (rhodopsin-like) family of G protein-coupled receptors. Binding of Ang II stabilizes an active receptor conformation that couples principally to Gq/11, activating phospholipase C and generating inositol trisphosphate and diacylglycerol, which in turn mobilize intracellular calcium and activate protein kinase C [3,4]. AT1R also couples to Gi and G12/13 proteins and activates numerous downstream cascades, including mitogen-activated protein kinases, Janus kinase/signal transducer and activator of transcription, and the small GTPases Rho and Rac [4]. In addition to classical G protein signaling, AT1R recruits β -arrestins, which mediate receptor internalization and initiate a distinct, G protein-independent signaling program with effects on cell survival and contractility [4,9]. A critical feature of AT1R in cardiovascular pathology is its capacity to activate membrane-bound NADPH oxidases, generating reactive oxygen species (ROS) that serve as second messengers and as mediators of vascular injury [10,11]. AT1R can also be transactivated by mechanical stretch in the absence of Ang II, a property that links hemodynamic load directly to receptor signaling and is relevant to pressure-induced vascular remodeling [12]. Agonistic autoantibodies directed against the second extracellular loop of AT1R can likewise activate the receptor and have been implicated in preeclampsia, transplant rejection and, experimentally, in accelerated atherosclerosis [13,14].

The physiological actions of Ang II at AT1R are counterbalanced by the angiotensin II type 2 receptor (AT2R) and by the angiotensin-converting enzyme 2 (ACE2)/angiotensin-(1–7)/Mas axis, which generally oppose the vasoconstrictive, proliferative and pro-oxidant effects of AT1R activation [15,16]. The balance between these opposing arms of the RAAS is an important determinant of vascular homeostasis.

3. Mechanisms Linking AT1R to Hypertension

3.1. Vasoconstriction and Sodium Homeostasis

The most immediate blood pressure-raising action of AT1R activation is vasoconstriction. Ang II-induced AT1R signaling in vascular smooth muscle cells (VSMCs) elevates intracellular calcium and sensitizes the contractile apparatus through the RhoA/Rho-kinase pathway, increasing peripheral vascular resistance [3,4]. At the level of the kidney, AT1R activation promotes sodium and water retention both directly, by enhancing proximal tubular sodium reabsorption, and indirectly, by stimulating aldosterone release from the adrenal cortex [17]. Elegant cross-transplantation experiments using Agtr1a-deficient mice demonstrated that AT1 receptors in the kidney are essential for the full hypertensive response to Ang II, establishing the renal AT1R as a dominant control point for long-term blood pressure regulation [17]. In these experiments, the chronic pressor response to Ang II was abolished when AT1 receptors were absent from the kidney, even when they were present elsewhere in the body, and conversely was preserved when renal AT1 receptors were intact despite their absence from extrarenal tissues. This demonstrated that, although AT1R is expressed ubiquitously, its action in the kidney is both necessary and largely sufficient for sustained hypertension, a conclusion with direct implications for the interpretation of AGTR1 variants that alter receptor density in a tissue-nonspecific manner.

3.2. Sympathetic and Central Actions

AT1R is expressed in circumventricular organs and other central nervous system regions that regulate autonomic outflow. Activation of central AT1R increases sympathetic nerve activity, enhances thirst and salt appetite, and stimulates vasopressin release, all of which contribute to the elevation of blood pressure [4]. Peripherally, AT1R activation on sympathetic nerve terminals facilitates noradrenaline release, amplifying vasoconstriction. The central and peripheral sympathetic actions of AT1R are particularly relevant to the atherosclerosis–hypertension interface, because heightened sympathetic tone not only raises blood pressure but also contributes to endothelial dysfunction, insulin resistance and a pro-inflammatory state, each of which independently accelerates atherogenesis. This neurogenic component may be especially important in the early, high-renin phases of hypertension and in conditions of chronic stress.

3.3. Oxidative Stress and Endothelial Dysfunction

A unifying mechanism linking AT1R to both hypertension and atherosclerosis is oxidative stress. Ang II is one of the most potent physiological activators of vascular NADPH oxidases, and AT1R-dependent generation of superoxide reduces the bioavailability of nitric oxide (NO), impairing endothelium-dependent vasodilation and promoting vasoconstriction [10,11,18]. The reaction of superoxide with NO generates peroxynitrite, which further damages the endothelium and uncouples endothelial NO synthase. Ang II, acting through AT1R and NADPH oxidase, also increases asymmetric dimethylarginine, an endogenous inhibitor of NO synthase, in VSMCs [19]. This oxidative, NO-deficient state raises vascular tone and blood pressure and simultaneously creates a pro-atherogenic endothelial phenotype, illustrating the mechanistic convergence of the two diseases [2,11].

Importantly, this coupling means that the same quantum of AT1R activation that elevates blood pressure also initiates the earliest cellular events of atherosclerosis, so that the two diseases are not merely associated through shared risk factors but are driven, in part, by a single shared receptor-level mechanism. The resulting feed-forward loop—hypertension begetting oxidative endothelial injury, which impairs vasodilation and further raises pressure—helps to explain the clinical difficulty of dissociating the vascular consequences of hypertension from those of atherosclerosis.

4. Mechanisms Linking AT1R to Atherosclerosis

4.1. Endothelial Activation and Leukocyte Recruitment

Beyond impairing NO-dependent vasodilation, AT1R activation induces a pro-inflammatory endothelial phenotype. Ang II upregulates adhesion molecules, including vascular cell adhesion molecule-1 and intercellular adhesion molecule-1, and chemokines such as monocyte chemoattractant protein-1, thereby promoting the recruitment and transendothelial migration of monocytes [20,21]. It also increases endothelial expression of the lectin-like oxidized LDL receptor-1 (LOX-1), enhancing uptake of oxidized LDL and amplifying endothelial dysfunction [22]. These actions mark the earliest stages of atherosclerotic lesion formation.

4.2. Vascular Smooth Muscle Cell Proliferation and Remodeling

AT1R is a powerful stimulus for VSMC hypertrophy, proliferation and migration, processes central to both hypertensive vascular remodeling and atherosclerotic plaque growth [4,10]. Ang II activates growth factor pathways, stimulates production of extracellular matrix proteins and matrix metalloproteinases, and promotes a phenotypic switch of VSMCs from a contractile to a synthetic, pro-atherogenic state [23]. In the media and neointima, these effects contribute to arterial wall thickening, reduced luminal diameter and plaque expansion.

4.3. Inflammation and Oxidation of Lipoproteins

Ang II promotes vascular inflammation through activation of the redox-sensitive transcription factor nuclear factor- κ B, which drives the expression of cytokines, chemokines and adhesion molecules [24]. AT1R-dependent ROS generation also facilitates oxidative modification of LDL within the arterial wall, a key step in foam cell formation [25]. The receptor is expressed on monocytes/macrophages and T lymphocytes, and Ang II modulates their activation, so that AT1R signaling operates in both the vessel wall and the infiltrating immune cells [26]. Studies in mice demonstrated that T cells are required for the full hypertensive and vascular inflammatory response to Ang II, linking AT1R signaling to adaptive immunity [26].

4.4. Plaque Instability and Thrombosis

AT1R activation influences the stability of established plaques. By stimulating matrix metalloproteinase activity and apoptosis of VSMCs and macrophages, Ang II can thin the fibrous cap and enlarge the necrotic core, predisposing to rupture [3]. Ang II also increases plasminogen activator inhibitor-1 expression, shifting the hemostatic balance toward thrombosis [27]. These mechanisms help explain why hypertension, in which AT1R signaling is often enhanced, is associated with an increased risk of acute atherothrombotic events. The destabilizing actions of Ang II are compounded by its effects on the vasa vasorum and on intraplaque angiogenesis, where AT1R-driven vascular endothelial growth factor expression can promote the formation of fragile neovessels prone to intraplaque hemorrhage, a recognized trigger of plaque progression and rupture.

4.5. Convergence of Hypertension and Atherosclerosis at the Level of AT1R

The mechanisms outlined in Sections 3 and 4 are not independent. Many of the molecular events triggered by AT1R activation contribute simultaneously to the elevation of blood pressure and to the progression of atherosclerosis, and this dual action distinguishes AT1R from mediators that act on only one of the two diseases. Oxidative stress generated by NADPH oxidase reduces NO bioavailability, which both raises vascular tone (hypertension) and promotes endothelial activation and lipoprotein oxidation (atherosclerosis) [2,11]. Vascular smooth muscle cell growth and matrix remodeling thicken and stiffen the arterial wall, increasing pulse-wave velocity and systolic pressure while contributing to neointima and plaque [23,28]. Inflammatory and immune activation, including the AT1R-dependent recruitment of T cells, amplifies both the hypertensive response and lesion inflammation [26]. Because hypertension increases wall tension and, through stretch-induced AT1R transactivation, can activate the receptor even in the absence of elevated Ang II [12], established hypertension can further stimulate the atherogenic program, creating a self-reinforcing relationship. This convergence provides a mechanistic rationale for why interventions that block AT1R might be expected to benefit both conditions, and it frames the shared genetic susceptibility discussed below.

5. AGTR1 Polymorphism and Cardiovascular Disease

5.1. The A1166C (rs5186) Variant

The most extensively investigated AGTR1 polymorphism is a transversion of adenine to cytosine at position 1166 in the 3'UTR (A1166C, rs5186). Bonnardeaux and colleagues first reported an association between the C allele and essential hypertension [29]. Subsequent work revealed a plausible molecular mechanism: the A1166C variant lies within a target site for microRNA-155, and the C allele disrupts miR-155-mediated repression of AGTR1, resulting in higher receptor expression [7,8]. Because increased AT1R density would be expected to amplify Ang II signaling, this provides a direct link between the genotype and the functional consequences described above. MicroRNA-155 normally binds to a complementary sequence in the AGTR1 3'UTR and represses translation; the presence of the C allele at position 1166 weakens this interaction, relieving repression and allowing more receptor protein to be synthesized from a given amount of messenger RNA [7,8]. This is a particularly instructive example

of a functional 3'UTR polymorphism, because it couples a common human variant to a defined regulatory microRNA and to a measurable change in receptor expression, bridging population genetics and receptor biology. Functional studies have supported this mechanism. Carriers of the C allele show enhanced vascular responsiveness to Ang II [30] and greater pressor sensitivity, and the variant has been associated with increased aortic stiffness [28]. The A1166C polymorphism has also been reported to interact with angiotensin-converting enzyme genotype in determining coronary risk [31].

5.2. Association with Hypertension

A large number of case-control studies have examined the relationship between A1166C and essential hypertension, with heterogeneous results. A HuGE review and several meta-analyses concluded that the C allele is associated with a modestly increased risk of hypertension, with the strongest signals in populations of European descent and weaker or absent associations in some Asian and African groups [32,33]. A more recent meta-analysis combining AGTR1 and CYP11B2 polymorphisms likewise identified AGTR1 A1166C as a significant genetic determinant of hypertension [34]. The modest effect size and between-study heterogeneity are typical of common variants influencing complex traits and reflect differences in allele frequency, environmental exposures and study design.

5.3. Association with Atherosclerotic Disease

The A1166C variant has been studied in relation to coronary artery disease (CAD), myocardial infarction and other atherosclerotic phenotypes. A systematic meta-analysis of the rs5186 polymorphism and coronary heart disease found a significant association between the C allele and increased risk, particularly under recessive and allelic genetic models [35]. A separate meta-analysis focusing on Chinese populations reached broadly similar conclusions [36]. The variant has also been associated with an increased risk of restenosis after percutaneous coronary intervention, consistent with the role of AT1R in neointimal proliferation [37]. Beyond rs5186, other AGTR1 variants and haplotypes have been examined, and some studies report associations with carotid atherosclerosis, left ventricular hypertrophy and diabetic vascular complications, although replication has been inconsistent [4]. Overall, the genetic data are consistent with the biology: variation that increases AT1R expression or signaling tends to raise the risk of both hypertension and atherosclerotic disease, but the effects of any single common variant are small and modified by genetic and environmental background. It is also important to recognize that AGTR1 does not act in isolation: variants in other RAAS genes, including those encoding angiotensinogen, renin, the angiotensin-converting enzyme and aldosterone synthase (CYP11B2), interact with AGTR1 and with environmental factors such as dietary sodium to shape the final phenotype [31,34]. Gene–gene and gene–environment interactions of this kind probably account for much of the heterogeneity observed across association studies, and they argue for integrated, pathway-level analyses rather than the study of individual polymorphisms in isolation.

6. Evidence from Experimental Models

Animal models have been central to establishing the causal role of AT1R in the shared pathophysiology of hypertension and atherosclerosis. Infusion of Ang II into hyperlipidemic apolipoprotein E-deficient (ApoE^{−/−}) mice markedly accelerates atherosclerosis and induces abdominal aortic aneurysms, effects that depend on AT1R [38,39]. Genetic deletion of the *Agtr1* receptor reduces lesion formation in hypercholesterolemic mice, and long-term studies confirmed a sustained reduction in atherosclerosis in AT1a-deficient animals [40,41].

An important question has been the cellular site at which AT1R acts. Bone marrow transplantation experiments demonstrated that AT1a receptors in the host vascular wall, rather than in bone marrow-derived cells, are essential for Ang II-induced atherosclerosis [42]. This finding localizes the critical receptor pool to the resident cells of the vessel wall and underscores the importance of local, as opposed to circulating or hematopoietic, RAAS activity. The concept of a local, tissue-based RAAS—in which angiotensinogen, renin and the angiotensin-converting enzyme are expressed within the arterial wall and generate Ang II *in situ*—has reshaped understanding of how the system drives chronic vascular disease, because it implies that pathological AT1R activation can occur locally even when systemic RAAS activity appears normal. Consistent with the role of oxidative stress, NADPH oxidase isoforms acting downstream of AT1R, including NADPH oxidase 1 and NADPH oxidase 4, contribute to Ang II-induced vascular remodeling, aneurysm formation and atherosclerosis in these models [43,44]. Furthermore, agonistic antibodies to AT1R accelerate atherosclerosis in ApoE^{−/−} mice, providing additional evidence that persistent receptor activation is pro-atherogenic independent of circulating Ang II [14]. Pharmacological blockade of AT1R or inhibition of renin reduces atherosclerosis in these models, often beyond what would be predicted from blood pressure lowering alone [40,45]. Collectively, these models provide strong causal evidence that AT1R activation is not merely a correlate but a driver of atherosclerosis, and that the resident vascular wall is the decisive site of action. They also caution against over-interpreting single cell-type knockouts, since depletion of AT1a from endothelial or smooth muscle cells alone does not always reproduce the protection seen with global deletion, implying redundancy and cooperative signaling among vascular cell populations [46].

7. Clinical Implications: AT1R Blockade in Hypertension and Atherosclerosis

The pivotal role of AT1R in cardiovascular disease is reflected in the widespread clinical use of angiotensin receptor blockers (ARBs), which selectively antagonize the receptor. ARBs are effective antihypertensive agents and reduce cardiovascular morbidity and mortality in high-risk populations. The LIFE trial showed that losartan reduced cardiovascular events, particularly stroke, more than atenolol at similar levels of blood pressure control in hypertensive patients with left ventricular hypertrophy, suggesting benefits beyond blood pressure reduction

[47]. The ONTARGET trial established that the ARB telmisartan was non-inferior to the angiotensin-converting enzyme inhibitor ramipril in reducing major cardiovascular outcomes in patients at high vascular risk [48]. Several imaging studies support a direct anti-atherosclerotic action of ARBs. Candesartan reduced carotid intima-media thickness in hypertensive patients, an effect attributed in part to enhanced NO bioavailability and reduced oxidative stress [49]. Comparative trials indicated that ARB-based regimens induce favorable patterns of carotid and left ventricular remodeling relative to β -blocker-based therapy [50]. By interrupting the AT1R-dependent cascade of oxidative stress, inflammation and VSMC proliferation, ARBs are mechanistically well positioned to retard atherogenesis while controlling blood pressure, consistent with the experimental data reviewed above [11,40]. The pleiotropic, blood pressure-independent effects of ARBs—improved endothelial function, reduced oxidative stress, attenuated inflammation and favorable arterial remodeling—are precisely those predicted from the dual role of AT1R in the two diseases, and they distinguish ARBs from antihypertensive agents that lower pressure without directly targeting the shared receptor-level mechanism. These agents thus exemplify how targeting a single receptor can simultaneously address two convergent diseases.

Pharmacogenetic analyses have asked whether AGTR1 genotype predicts the response to RAAS blockade. Some studies suggest that the A1166C genotype influences the blood pressure response to ARBs or angiotensin-converting enzyme inhibitors, raising the possibility of genotype-guided therapy, although the evidence is not yet sufficient to inform routine clinical practice [4,51]. The interindividual variability in treatment response underscores the complexity of the RAAS and the influence of genetic background.

Table 1 summarizes the principal mechanisms through which AT1R activation contributes jointly to hypertension and atherosclerosis.

Table 1. Shared and distinct consequences of angiotensin II type 1 receptor (AT1R) activation in hypertension and atherosclerosis.

AT1R-mediated process	Contribution to hypertension	Contribution to atherosclerosis
Vasoconstriction (Ca^{2+} influx, Rho-kinase)	Increased peripheral resistance	Altered wall shear stress
Renal sodium and water retention; aldosterone release	Expanded volume, sustained pressure	Indirect, via pressure load
NADPH oxidase activation and reactive oxygen species	Reduced nitric oxide, raised tone	Lipoprotein oxidation, endothelial activation
Endothelial adhesion molecule and chemokine expression	Endothelial dysfunction	Monocyte recruitment, early lesion formation
Vascular smooth muscle proliferation and matrix remodeling	Arterial stiffening	Neointima and plaque growth
Inflammatory and T-cell activation	Amplified pressor response	Plaque inflammation
Matrix metalloproteinase activity; plasminogen activator inhibitor-1	—	Plaque instability, thrombosis

8. Knowledge Gaps and Future Directions

Despite substantial progress, several questions remain. First, although the A1166C polymorphism has a plausible mechanistic basis through disruption of miR-155 regulation, the modest and heterogeneous associations across populations indicate that its clinical utility as a single marker is limited; large, ancestry-diverse studies and polygenic approaches integrating multiple RAAS variants are needed [32,34]. Second, the relative contributions of AT1R signaling in different cell types—endothelial cells, VSMCs, renal tubular cells and immune cells—to the combined hypertensive and atherosclerotic phenotype require further dissection using conditional genetic models, especially given reports that cell-specific deletion of AT1a does not always reproduce the effect of global deletion [46]. Third, the therapeutic potential of biased AT1R ligands, which selectively engage protective β -arrestin pathways while blocking harmful G protein signaling, remains to be established in atherosclerosis [9]. Fourth, the interplay between the AT1R axis and the protective ACE2/angiotensin-(1–7)/Mas axis offers opportunities for intervention that are not yet fully exploited [16]. Finally, the role of AT1R autoantibodies in human atherosclerosis, as distinct from classical ligand-mediated signaling, deserves systematic investigation [14].

9. CONCLUSIONS

The AGTR1 gene and its product, the angiotensin II type 1 receptor, occupy a central position in the intertwined pathogenesis of systemic hypertension and atherosclerosis. Through a broad repertoire of signaling pathways, AT1R activation raises blood pressure by driving vasoconstriction, sodium retention and sympathetic activation, while simultaneously promoting atherosclerosis through oxidative stress, endothelial dysfunction, inflammation, vascular smooth muscle proliferation and plaque destabilization. These shared mechanisms explain the frequent coexistence and mutual reinforcement of the two conditions. Functional variation in AGTR1, exemplified by the

A1166C polymorphism that increases receptor expression by disrupting microRNA-mediated regulation, modestly influences susceptibility to both hypertension and atherosclerotic disease, consistent with the receptor biology. Experimental models confirm that AT1R in the vascular wall is required for angiotensin II-driven atherosclerosis, and clinical use of angiotensin receptor blockers demonstrates that antagonizing this receptor lowers blood pressure, reduces cardiovascular events and can slow atherosclerotic progression, in part independently of blood pressure. A fuller understanding of cell-specific AT1R signaling, of genetic modifiers, and of the balance between the AT1R and the protective arms of the renin–angiotensin system should guide the development of more precise strategies to interrupt the common pathway that links hypertension to atherosclerosis.

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Conflicts of Interest

The author declares no conflicts of interest.

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