This Review is part of a thematic series on **Angiotensin-Converting Enzyme**, which includes the following articles:

Six Truisms Concerning ACE and the Renin-Angiotensin System Educed From the Genetic Analysis of Mice
Angiotensin-Converting Enzyme II in the Heart and the Kidney
Signaling by the Angiotensin-Converting Enzyme
ACE Polymorphisms

Angiotensin-Converting Enzyme and Vascular Remodeling

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Angiotensin-Converting Enzyme and Vascular Remodeling

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***Abstract*—**Vascular remodeling is the result of a close interplay of changes in vascular tone and structure. In this review, the role of angiotension-converting enzyme (ACE) and the impact of ACE inhibition on vascular remodeling processes during vascular injury and restenosis, hypertension, atherosclerosis, and aneurysm formation are discussed. The role of ACE and angiotensin II (Ang II) in neointimal thickening has been firmly established by animal studies and is mediated by Ang II type 1 (AT_1) receptor signaling events via monocyte chemoattractant protein-1 and NAD(P)H oxidase. ACE and Ang II are involved in the remodeling of large and resistance arteries during hypertension; here, cell proliferation and matrix remodeling are also regulated by signaling events downstream of the AT_1 receptor. In atherosclerosis, Ang II is involved in the inflammatory and tissue response, mediated by various signaling pathways downstream of the AT_1 receptor. Although ACE inhibition has been shown to inhibit atherosclerotic processes in experimental animal models, results of large clinical trials with ACE inhibitors were not conclusive. Remodeling of vessel dimensions and structure during aneurysm formation is counteracted by ACE inhibition. Here, a direct effect of ACE inhibitors on matrix metalloproteinase activity has to be considered as part of the working mechanism. The role of ACE2 in vascular remodeling has yet to be established; however, ACE2 has been shown to be associated with vascular changes in hypertension and atherosclerosis. **(*Circ Res*. 2007;101:441-454.)**

Key Words: vascular remodeling ■ angiotensin-converting enzyme ■ hypertension ■ atherosclerosis ■ restenosis

The vascular wall is continuously exposed to hemodynamic forces such as luminal pressure and shear stress. Alterations in these forces, either physiological or pathological, lead to functional and/or structural alterations of the vascular wall. Acute changes in hemodynamic forces can modify vessel diameter. Chronic changes in hemodynamic forces result in structural alterations of the vessel wall, indicated by changes in wall diameter and thickness. In addition, changes in vascular structure are not solely determined by hemodynamic forces,[1] and a role for inflammatory responses and changes in extracellular matrix components has been suggested.[2] Structural changes of the medial layer of the vascular wall during hypertension were termed "remodeling"[3–6] and subsequently translated to other vascular pathologies (Figure 1). The schematic representation is slightly adapted because in these pathologies, structural alterations of the intimal layer of the vascular wall contribute to total vessel wall mass. Thus, outward remodeling during atherosclerosis compensates for the plaque growth and postpones progression to flow-limiting stenosis, whereas during restenosis, intimal hyperplasia and constrictive remodeling result in luminal narrowing. It has been generally accepted and acknowledged that vascular remodeling is an important determinant in vascular pathologies.[2,7,8]

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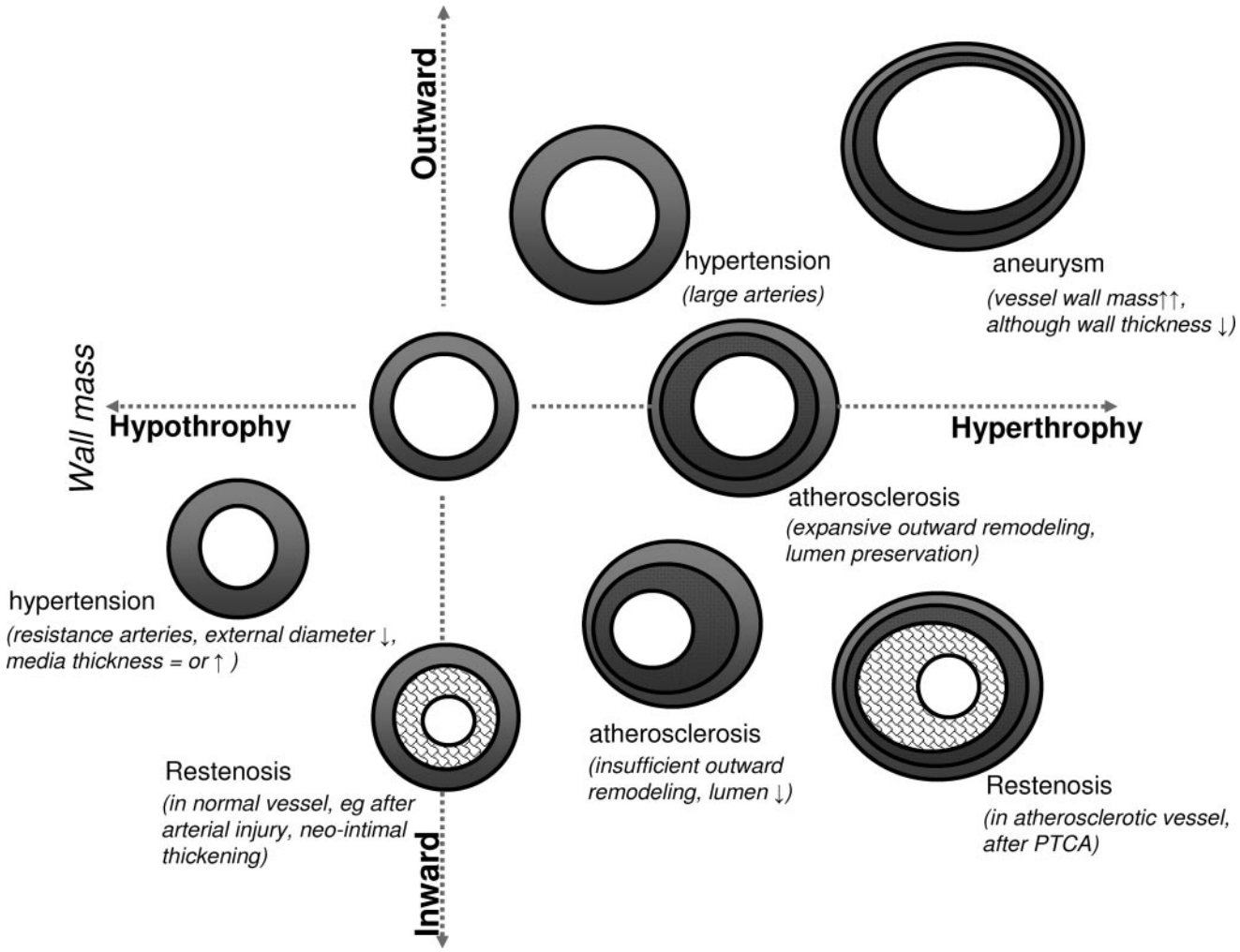

Figure 1. Diagram showing remodeling features and its effect on vessel wall mass and lumen during various pathophysiological conditions. Adapted from a previously published report.[8]

Remodeling of the vascular wall is the result of changes in both the cellular and noncellular components. Depending on the pathological process (Figure 1), smooth muscle cell (SMC) growth and migration, endothelial cell dysfunction, inflammation, extracellular matrix synthesis, or degradation are present.

Patients with essential hypertension are routinely treated with calcium channel blockers, diuretics, and angiotensin-converting enzyme (ACE) inhibitors. Several of these therapeutic agents are capable of (partially) correcting the remodeling of small arteries and arterioles that are seen in these patients,[9] and this is particularly true for the ACE inhibitors. ACE plays a key role in the renin–angiotensin system (RAS), as it generates the active octapeptide angiotensin (Ang) II from the decapeptide angiotension I. Ang II is the most well-known active peptide of the RAS, with very diverse functions. It is a potent vasoconstrictor but is also involved in inflammatory processes, cell growth, and matrix deposition and can lead to a prothrombotic state (reviewed elsewhere[10]). Given these functions, Ang II is considered a regulatory factor in the changes in wall structure and function during vascular remodeling.

In this review, after a short introduction on the effects of ACE on vascular function and signaling pathways, the role of ACE and the impact of ACE inhibition on vascular remodeling are discussed. Because "remodeling of the vessel wall" has diverse characteristics in different vascular pathologies, the role of ACE is discussed separately for remodeling during neointimal thickening/restenosis, hypertension, atherosclerosis, and aneurysm formation.

Vascular Effects of ACE and Downstream Signaling Pathways

The vascular effects of ACE are summarized in Table 1. Ang II, produced locally by endothelial ACE, is one of the key substances that affects endothelial function (or dysfunction). Ang II is a potent vasoconstrictor and is also able to induce other vasoconstrictors (see Table 1). In addition, ACE reduces vasodilation via degradation of bradykinin, a potent vasodilator (direct and indirect through reduced release of endothelium-derived NO and prostacyclin). This dual effect of ACE, generation of a vasoconstrictor and degradation of a vasodilator, is important in the regulation of vascular tone by the RAS. These effects of ACE are reflected by the signaling

TABLE 1. ACE, ACE2, and Their Substrates and Products

	Substrate	Generated Peptide or Result	Vascular Effects
ACE	Ang I	Ang II	Vasoconstriction (direct and via norepinephrine and endothelin-1[157]); reactive oxygen species production (leading to reduced NO bioavailability[158,159]); SMC hypertrophy/hyperplasia[160,161]; SMC migration and reduction of SMC apoptosis,[162,163] matrix deposition,[164,165] prothrombotic effects,[10] vascular permeability (through induction of cyclooxygenase-2, prostaglandins, and vascular endothelial growth factor,[166,167] endothelial [dys]function,[109,110] adhesion molecules,[16–18] increased lipid uptake[101,108]
	Bradykinin	Degradation	Reduced vasodilatory capacity[168,169]; antihypertrophic effects abolished[170]; most likely mediated by NO and prostacyclins[171]
	Ac-SDKP	Degradation	Reduced endothelial cell proliferation,[172] migration, and tube-formation[173]
	Ang(1–9) ?	Ang(1–7)?	See below
ACE2	Ang I	Ang(1–9)	Shown in vitro, unlikely to be very critical in vivo because of the very low catalytic efficiency[147]
	Ang II	Ang(1–7)	Ang(1–7) results in vasodilation[174–176] but is dependent on dose and artery; it may also be vasoconstrictive[177]; inhibition of cell proliferation[152]
	des–Arg9– and des–Arg10–Lys–bradykinin	Degradation	Reduced binding of these kinin metabolites on B_1 receptor (B_1 receptor expressed during inflammatory events, increased leukocyte adhesion, thought to mediate vasodilation primarily)[178]
	Apelin 13/36	Degradation	Reduced binding to APJ receptors (apelin peptides are considered hypotensive and cardioprotective)[179]
	Opioid peptides	Degradation	Reduced binding to opioid receptors (opioid receptors may have negative effects on cardiac contractility)[180]

pathways that are activated by Ang II and bradykinin (Figure 2). Although several angiotensin receptors have been described, this review focuses on the physiological and pathological effects during vascular remodeling that are mediated via the Ang II type 1 (AT_1) receptor. The AT_1 receptor signals through small GTP-binding proteins. Each of these small G proteins has key roles in specific cell functions. The Ras family regulates gene expression, the Rho family regulates cytoskeletal reorganization and gene expression, and the Rac family controls membrane ruffling and cell spreading.[11,12] Figure 2 shows a selection of the up- and downstream signaling pathways of these small G proteins in relation to the AT_1 receptor. Upstream are several tyrosine kinases, such as src and JAK2/Tyk, which have been shown to be pivotal to Ang II signaling pathways.[13] Downstream are the mitogen-activated kinases (MAPK) and signal transducers and activators of transcription (STATs).[11] Through these signaling cascades, Ang II initiates tissue remodeling via induction of SMC hypertrophy, hyperplasia, and migration and extracellular matrix production and synthesis of proinflammatory mediators. An important costimulatory event is the AT_1 receptor–dependent activation of NAD(P)H oxidase by Ang II.[14,15] This produces reactive oxygen species (ROS) (and reduces NO bioavailability) and initiates myriad other signaling events and activation of transcription factors such as Nuclear Factor κB and Activator Protein-1 (Figure 2). These transcription factors can induce multiple mediators of leukocyte recruitment, such as expression of selectins (E- and P-selectin) and integrins (β-2, α-4 integrin, and VLA-4)[16–18] and proinflammatory molecules such as monocyte chemoattractant protein 1 and interleukin (IL)-6.[19,20] In SMCs, Ang II can also directly activate nuclear factor κB, most likely via degradation of IκBs.[21]

Finally, ACE itself is also linked to a signaling cascade. In endothelial cells, binding of ACE inhibitors to ACE increases casein kinase 2–mediated phosphorylation of ACE, which activates ACE-associated JNK, most likely through mitogen-activated kinase kinase 7 (MKK7). JNK phosphorylates c-Jun and via activator protein-1, ACE, and cyclooxygenase-2 are transcribed (reviewed elsewhere[22]).

ACE and Neointimal Thickening/Restenosis

In the balloon-injured rat carotid, the developing neointima expressed high levels of ACE.[23] In another model of cuff-induced neointima formation in the femoral artery of mice, ACE expression was again increased in the neointimal, medial, and periadventitial area of the cuffed artery.[24] The effect of ACE on vascular remodeling was first established by a study of Morishita et al,[25] in which in vivo gene transfer of ACE in a normal, uninjured rat carotid artery resulted in increased wall-to-lumen ratios, indicative of the development of vascular hypertrophy. A follow-up study by the same group, using an antisense oligonucleotide against ACE in a rat vascular injury model, showed a significant decrease in neointima formation.[26]

The mechanisms by which ACE and Ang II can induce neointimal thickening or restenosis are only partly elucidated. The AT_1 receptor has been shown to play a central role. Neointimal AT_1 receptor expression increased in the rat model of carotid injury, even 24 weeks after injury. AT_1 receptor blockade inhibited neointimal thickening and collagen and elastin accumulation.[27] In monkeys and rabbits, AT_1 receptor blockade also reduced in-stent restenosis, oxidative stress, proinflammatory factors (MCP-1, IL-1β, and tumor necrosis factor-α) and NAD(P)H oxidase subunits (p22-phox, gp99-phox). These molecules are downstream of the AT_1

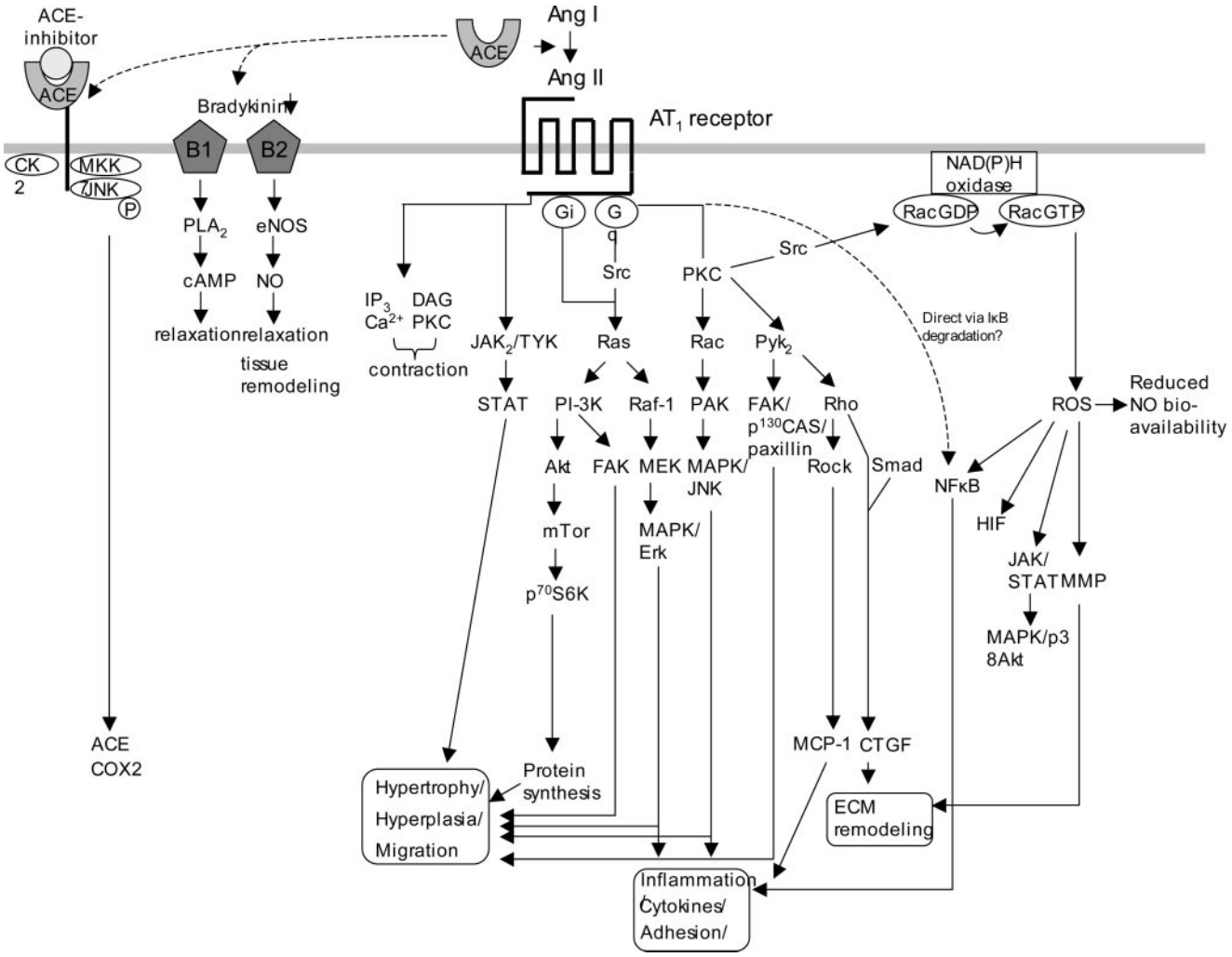

Figure 2. Signaling pathways of the AT_1 receptor, bradykinin (BK) receptors, and ACE. Adapted from previously published reports.[11–14,21,22,155,156]

receptor (Figure 2), suggesting that AT_1 receptor signaling is involved in neointimal formation.[28] Finally, protein kinase C is downstream of the AT_1 receptor and one of its iso-forms, protein kinase C-ζ was shown to be essential in normal and Ang II–accelerated neointimal growth after vascular injury. Inhibition of protein kinase C-ζ attenuated medial cellularity and expression of inflammatory mediators.[29]

ACE inhibitors have been shown to inhibit neointima formation in response to vascular injury in several models and species, such as in balloon-induced vascular injury in rats[30] and guinea pig,[31] in allograft-induced intima formation in rats,[32] and cuff-induced neointima formation in mice.[24,33] Several follow-up studies in these models showed that the favorable effects of ACE inhibition could be attributed, in part, to the bradykinin/endothelial NO synthase pathway and/or oxidative stress/NAD(P)H pathway.[33–35]

However, not all studies showed a beneficial effect of ACE inhibition after vascular injury. In rabbits, ACE inhibition with cilazapril did not reduce or prevent neointima formation after injury to the carotid artery,[31] and similar negative results were found in baboons.[36] Moreover, in large clinical trials (MERCATOR, MARCATOR), low antihypertensive doses of cilazapril did not prevent restenosis nor had favorable effects on overall clinical outcome after percutaneous transluminal coronary angioplasty (PTCA).[37,38] These studies suggest that inhibition of ACE is ineffective in inhibiting restenosis in patients following PTCA.

The lack of effect of ACE inhibition on restenosis in patients after PTCA was unexpected, and the possible causes for this discrepancy have been discussed extensively in literature. Firstly, the animal models used are different from the human situation. In the rat carotid injury model, "restenosis" is a misnomer and actually a neointima formed after an injury to a normal vessel, whereas in the human situation, a significant plaque burden leading to stenosis is already present before the injury.[39] Thus, fundamental differences in pathophysiology could explain the discrepancy in the outcome of clinical trials and preclinical studies in animal models for ACE inhibition in restenosis. Secondly, there may be a dose effect. Rakugi et al showed that there was a dissociation of the ability of an ACE inhibitor to decrease blood pressure and circulating ACE activity from its ability to inhibit tissue ACE. It was shown that the dose necessary to inhibit neointima formation was higher than the hypotensive

dose. Thus, higher doses of ACE inhibitors may be needed to inhibit tissue ACE and prevent restenosis in patients.[40] Thirdly, there is a remarkable species variation in the activity of non–ACE-dependent conversion of Ang I to Ang II.[41] It has become clear that ACE is not the only enzyme that can generate Ang II. In studies by Okunishi et al,[42,43] evidence was presented that in blood vessels of various species, a unique enzyme was present that converts Ang I in Ang II. This enzyme was later identified as chymase. In a follow-up study, Okunishi et al showed that vascular expression of chymase differed between species. In human arterial strips, treatment with captopril blocked 30% to 40% of the conversion of Ang I to Ang II, whereas inhibition of chymase by chymostatin blocked 60% of Ang II generation. In rabbit arteries, however, captopril induced >90% inhibition and chymostatin had minimal effect.[44] Also, Jin et al reported that the ratio of ACE- and chymase-dependent Ang II formation is even different in various blood vessels of the same species.[45] This site specificity could also explain the fact that studies in humans showed an exclusive ACE dependency of local Ang II generation in the forearm,[46] although the study by Okunishi et al described above showed a 60% chymase dependency in human gastroepiploic arterial strips.[44]

In conclusion, ACE inhibition was not effective in inhibiting restenosis in patients after PTCA. Although several issues still need to be resolved (eg, fundamental differences between animal models and human disease; species- and vessel-type-specific expression of chymase; and dosage of ACE inhibitor), the results of clinical trials were unexpected to some extent and do not advocate the use of ACE inhibitors in these patients. This does not exclude the important role of Ang II in the development of restenosis. Experimental studies have shown that the AT_1 receptor and downstream pathways are involved in neointima formation; moreover, selective angiotensin receptor blockers may be effective in preventing restenosis in patients with complex lesions. In the Val-PREST trial, it was shown that restenosis was only 19% in valsartan-treated patients, compared with 39% in the control group.[47]

ACE and Vascular Remodeling During Hypertension

Remodeling of the Large Conduit Arteries

During essential hypertension, the large arteries exhibit an increased lumen size, a thickened media with increased collagen deposition, and decreased compliance.[4,48,49] The thickening of the arterial wall is considered to be one of the main compensatory mechanisms to preserve circumferential wall stress.[50] In hypertensive patients, carotid pulse pressure was a strong independent determinant of carotid artery enlargement and wall hypertrophy, whereas mean blood pressure and brachial pulse pressure were not, indicating the strong influence of local pulsatile mechanical load.[51] The outward hypertrophic vascular remodeling is progressive because it increased with age in the carotid artery of patients with untreated essential hypertension.[52] Hypertension is clearly associated with increased cardiovascular morbidity and mortality, and it is thought that vascular hypertrophy leads to increased atherosclerotic disease at arterial sites such as the carotid artery.[53]

The RAS has been clearly implicated in hypertension-induced large artery hypertrophy. Ang II–induced SMC hypertrophy and collagen deposition (Table 1) have been shown in hypertensive animal models.[54,55] More recently, attention was also directed toward the effect of inflammation and endothelial dysfunction during hypertension. It is likely that the RAS, and more specifically Ang II, is also involved in cytokine excretion, inflammatory cell adhesion, and endothelial dysfunction during hypertension-induced remodeling of the large arteries (Table 1 and Kakar and Lip[56]).

There is conflicting evidence regarding the increase in ACE expression in the vascular wall during experimental hypertension. Most reports have shown an increase in vascular ACE expression in 2-kidney, 1-clip–induced hypertension[57–59] and spontaneous hypertensive rats (SHRs),[60] although Jandeleit et al did not find altered ACE concentrations in the resistance arteries of SHRs.[61] However, ACE inhibitors have been shown to induce a significant regression in large artery hypertrophy both in animals with hypertension[54,55,62] and hypertensive patients.[63–65] These studies mainly focused on effects on the large elastic conduit arteries, but Girard et al showed that smaller, more muscular arteries also benefited from ACE inhibition. In this study, it was shown that long-term ACE inhibition by perindopril not only improved carotid artery compliance but also reduced radial artery hypertrophy.[66] Also, Armentano et al recently showed that ACE inhibition resulted in improved wall energetics and wall stress by reducing SMC activation and vessel wall remodeling. These findings suggests that ACE inhibition also protects vascular function and is able to reduce extra load on the heart.[67]

ACE and Remodeling of Resistance Arteries During Hypertension

In contrast to the outward hypertrophic remodeling of the large arteries during hypertension, small (resistance) arteries exhibit a smaller lumen and external diameter, a normal or increased media thickness and an increased media-to-lumen ratio.[49] SMC hypertrophy or hyperplasia may be present depending on the species, vascular bed, or severity of the disease. In hypertensive patients, a rearrangement of SMCs around a smaller lumen was shown,[68] but in patients with renovascular hypertension, remodeling of resistance arteries resulting from SMC hypertrophy was also present.[69] Changes in extracellular matrix content are also involved in this remodeling, as collagen and fibronectin deposits were found in the resistance arteries of experimental models and patients with hypertension.[70] Remodeling of the resistance arteries during hypertension may be one of the first signs of organ damage found in mild hypertension in humans. It preceded the development of left ventricular hypertrophy and thickening of the intima–media of the large conduit arteries.[71]

Small artery remodeling is involved in the clinical complications of hypertension, such as stroke, nephroangiosclerosis, and myocardial infarction.[49] Pulse pressure was shown to be the most important determinant of small artery remodeling in elderly patients with mild essential hypertension.[71] In con-

trast, in younger patients, small artery remodeling correlated with diastolic pressure. Thus with age, the cause of small artery remodeling changes and pulse pressure becomes an important determinant of increased cardiovascular risk and vascular damage (reviewed elsewhere[49]).

The involvement of the RAS in these remodeling features has been investigated in both experimental studies and studies in hypertensive patients. ACE inhibition was effective in correcting vascular structure and decreasing medial collagen deposition in experimental models.[72–76] Studies in patients with hypertension treated with ACE inhibitors gave similar beneficial effects in the correction of resistance artery structure. ACE inhibitors proved to be more effective than β-blockers (atenolol) for both structural[77–80] and functional alterations of these resistance arteries.[81]

The downstream events of ACE in the remodeling of resistance arteries have also been partly elucidated. In SHRs, ACE inhibitors or AT_1 receptor antagonists reduced blood pressure and vascular activity of p42/p44 MAPKs (or extracellular signal-regulated kinase 1/2), which are downstream of AT_1 receptor–induced Ang II signaling (Figure 2).[82] Extracellular signal-regulated kinase 1/2 inhibition improved endothelial function and attenuated Ang II–induced contractility of mesenteric resistance arteries, suggesting that part of the Ang II–induced changes in vascular function are mediated by downstream MAPKs.[83]

In Ang II–infused mice, an NAD(P)H oxidase inhibitor (apocynin) reduced the blood pressure elevation and prevented structural alterations, endothelial dysfunction, and collagen deposition in the media of small mesenteric arteries, indicating that downstream NAD(P)H oxidase activity is involved in Ang II–induced functional and structural alterations of the vascular wall.[84]

Finally, in small subcutaneous resistance arteries of mild hypertensive patients, long-term AT_1 receptor blockade (1 year) was able to decrease the media-to-lumen ratio. In a parallel group of patients treated with a calcium channel blocker (amlodipine), media-to-lumen ratio continued to increase. AT_1 receptor blockade also prevented increases in transforming growth factor-β and connective tissue growth factor expression and collagen III and IV deposition. All of these parameters continued to increase in amlodipine-treated patients.[85] Interestingly, connective tissue growth factor was shown to be downstream of the AT_1 receptor (Figure 2) and is considered a novel mediator of Ang II–induced vascular fibrosis.[86] Thus, in human resistance arteries, AT_1 receptor blockade, but not calcium channel blockade, affected fibrosis, possibly via a connective tissue growth factor–mediated pathway.

The paradigm of beneficial effects of ACE inhibition on vascular remodeling compared with the relative neutral effects of other antihypertensive therapies and whether or not the blood pressure reduction is involved are still the subject of intense investigations. Experimental studies have shown that Ang II caused vascular hypertrophy in part by a nonpressor mechanism. Cotreatment with the vasodilator hydralazine prevented the rise in pressure but not the vascular changes.[87] Also, the in vivo gene transfer studies by Morishita et al showed that local expression of ACE induced vascular hypertrophy independent of blood pressure changes.[25] Analyses in hypertensive patients, however, showed that the cardiovascular protection induced by antihypertensive drugs was determined by the change in systolic blood pressure, and a minor change in blood pressure (≈3 mm Hg) was sufficient to explain the cardiovascular benefits.[88,89] This was (partly) challenged by an accompanying analysis of the ASCOT trial,[90] which suggested that the amlodipine with or without perindopril treatment regimen had a benefit that extended beyond blood pressure. Although the authors themselves and an editorial[89] suggested statistical adjustments as an explanation, it remains possible that effects of the treatment regime on other variables could contribute to the differences in cardiovascular event rates.

ACE and Atherosclerosis

Atherosclerosis is a complex, progressive disease of the large systemic arteries and the leading cause of death in the western world. This multifactorial disease is characterized by the accumulation of lipids, cells, and extracellular matrix in the vessel wall. Recent research has shown that inflammation and cytokine pathways are crucial in the development and progression of atherosclerotic lesions. Immune cells are already present in early lesions and cytokine pathways are involved in every stage of the disease. Both animal and human studies have shown that hyperlipidemia results in endothelial activation, which enables infiltration and retention of LDL in the arterial intima. An inflammatory response is initiated in which increased expression of adhesion molecules on the activated endothelium attract leukocytes. Monocytes migrate in the vessel wall, differentiate in macrophages that take up modified LDL, and initiate a tightly regulated network, resulting in a cascade of cytokine secretion. This attracts more inflammatory cells, including T cells. Activated T cells will secrete proinflammatory cytokines and control atherosclerotic plaque inflammatory reactions, also by negative feedback loops, such as secretion of antiinflammatory cytokines by T-regulatory cells.[91] There is convincing evidence that Ang II is involved in several important steps of the inflammatory processes during atherosclerosis, such as the increase in vascular permeability and the infiltration of leukocytes. Ang II is also involved in LDL oxidation and uptake, as well as thrombosis (Table 1).

ACE is abundantly expressed in vulnerable lesions and is localized in macrophage foam cells, present in the shoulder region, the endothelial cells of neovessels and spindle-shaped SMCs.[92–94] Fukuhara et al also showed ACE expression in foam cells and lymphocytes of human carotid atherosclerotic lesions.[95]

Hoshida et al measured ACE activity in coronary atherectomies of patients with acute symptoms and stable ischemic heart disease with and without restenosis. Interestingly, ACE activity was significantly increased in the culprit coronary lesions of patients with acute coronary syndrome compared with patients with stable ischemic heart disease.[96]

Intervention studies in atherosclerotic animal models have shown the atherogenic effect of Ang II and the antiatherogenic effect of ACE inhibitors. Continuous administration of Ang II to $ApoE^{-/-}$ mice significantly increased lesion size.[97,98]

In atherosclerotic lesions induced by an extravascular device consisting of a tapered collar, Ang II treatment also induced a more vulnerable lesion phenotype, with evidence of intraplaque hemorrhages.[99] Interestingly, hypercholesterolemia itself increased plasma angiotensinogen and Ang II concentrations.[100] This observation suggests that there may be a positive feedback loop between high cholesterol levels and Ang II, in which high cholesterol levels increases Ang II, and Ang II, in turn, increases lipid uptake.[101]

The protective actions of ACE inhibitors on atherogenesis have been shown in a number of experimental models. In ApoE$^{-/-}$ mice, fosinopril and captopril inhibited LDL oxidation and reduced atherosclerotic lesion size.[102,103] The same protective effects were shown in atherosclerotic minipigs[104] and hyperlipidemic rabbits[105,106] and monkeys.[107] ACE inhibition was also effective in reducing LOX-1 expression in mammary artery biopsies of patients with coronary artery disease.[108] Finally, ACE plays an important role in endothelial dysfunction. This is supported by studies in patients with coronary artery disease, showing that ACE inhibitors improved endothelial dysfunction, as measured by flow-mediated dilation of the brachial artery.[109,110]

The mechanisms by which Ang II can initiate or deteriorate atherosclerosis are partly elucidated. In an elegant study by Cassis et al, using bone marrow transplantation in AT_1 subtype a (AT_{1a}) receptor knockout and wild-type mice, it was shown that the AT_{1a} receptor has an important role in the development of Ang II–induced atherosclerosis and aneurysm formation. More specifically, AT_{1a} receptor expressed on bone marrow–derived cells resulted in a modest reduction of Ang II–induced atherosclerosis, whereas the presence of this receptor in the vascular tissue of the recipient was required for the initiation of Ang II–induced atherosclerosis and aneurysms.[111] Other studies showed that MCP-1 is an essential inflammatory mediator in Ang II–induced progression of atherosclerosis. Thus, blockade of MCP-1 limited Ang II–induced progression of atherosclerotic lesions in ApoE$^{-/-}$ mice and suppressed the induction of proinflammatory cytokines such as tumor necrosis factor-α and IL-6.[112] Moreover, this was shown to be dependent on the MCP-1 receptor CCR2 because in CCR2 knockout mice, Ang II–induced cell proliferation, increased wall thickness, and perivascular fibrosis were reduced.[113] These studies confirm the important role of MCP-1 as one of the downstream molecules of Ang II–induced activation of the AT_1 receptor (Figure 2).

Recently, Kunieda et al suggested another mechanism by which Ang II can accelerate atherosclerosis. In their study, it was shown that Ang II promoted vascular inflammation by inducing premature senescence of SMCs. This pathway was p53/p21 dependent, and p53/p21 inhibition suppressed the induction of proinflammatory cytokines (such as IL-6 and IL-1β), cellular senescence, and the development of atherosclerosis.[114]

ACE Inhibition in Patients With Coronary Artery Disease: Clinical Trials

Several large clinical trials have been conducted in which the "antiatherosclerotic" effect of ACE inhibition was studied in patients with cardiovascular disease. Outcomes, however, were variable (see Table 2). In both the HOPE and EUROPE[115,116] trials, reduced rates of death from cardiovascular causes were found in patients treated with an ACE inhibitor. Other trials, however, showed no reduction in the incidence of major end points (QUIET,[117] PEACE,[118] QUASAR,[119] PART-2,[120] SCAT[121]). This discrepancy with the overall positive effects of experimental studies in which ACE inhibition proved to be antiatherogenic is similar to what was seen in studies on ACE and remodeling during intimal thickening. Apparently, the complex nature of the disease is not fully represented in the various animal models, and it is likely that therapeutic intervention in a single pathway is not sufficient to reduce the clinical manifestations in patients.

Recent metaanalyses concluded that the use of ACE inhibitors should be considered in all patients with vascular disease.[122–124] However, there were some differences in patient characteristics in the trials used in the metaanalyses, especially with respect to cardiovascular risk. Although HOPE and EUROPE showed that ACE inhibitors lowered cardiovascular morbidity in patients with atherosclerosis and preserved left ventricular function, the PEACE study detected no benefit of ACE inhibition. The PEACE study population had a lower cardiovascular baseline risk (fewer patients with diabetes and high cardiovascular risk), lower arterial blood pressure, and LDL-cholesterol, and patients were treated more frequently with statins and antiplatelet drugs. Thus, as various editorials also pointed out,[125,126] what the PEACE study showed was that ACE inhibitors could be beneficial for patients with more risk factors (such as high serum lipids, diabetes mellitus) but may offer modest (to no) extra benefit for patients with low-risk factors or those that are already treated with statins and antiplatelet drugs. From the clinical studies, it can be concluded that aggressive risk factor modification in patients with atherosclerosis is still the primary goal and not all patients may need treatment with ACE inhibitors.

ACE and Aneurysm Formation

An aneurysm is defined as a permanent dilation of the arterial wall, which is characterized by outward vessel remodeling, both in vessel dimension and vascular structure. Most aneurysms are asymptomatic and undiagnosed: however, at diameters exceeding 5.5 cm, the risk of rupture increases considerably.[127] The underlying problem is weakening of the aortic wall, progressive dilation, and, if left untreated, aortic rupture. Treatment for dilated aneurysms (>5.5 cm) is conventional surgical and endovascular repair and therapeutically much is to be gained for the smaller aneurysms (<5 cm). During aneurysm formation, processes such as proteolysis, inflammation, and oxidant formation are important, and these are also the mechanisms in which ACE and ACE generated regulators are involved.[128]

ACE is expressed in the aneurysmal vascular wall, both in human disease and animal models. In aneurysmal aortic specimens obtained during operative repair in patients, ACE activity was increased 6-fold. ACE-positive cells (by immunohistochemical staining) were mainly macrophages, both in the media and the intima. Chymase activity was also signif-

TABLE 2. Comparison of the Effects of ACE Inhibitors in Patients With Cardiovascular Disease

Name of Study	No. of Patients	ACE Inhibitor	Follow Up	End Points (Selection of)	Result	Ref
QUIET	1750	Quinapril, 10–20 mg/day	27 mo	Cardiac death, resuscitated cardiac arrest, nonfatal MI (among others)	No difference in primary outcome (38% in both groups)	117
HOPE	9297 (patients with 2 risk factors)	Ramipril, 10 mg/day	5 yr	MI, stroke, death	14% of patients receiving ramipril compared to 17.8% of controls reached the primary end points (significant difference)	116
EUROPA	13655 (lower-risk patients)	Peridoril, 8 mg/day	3 yr	Cardiovascular death, nonfatal MI, resuscitated cardiac arrest	8% of patients receiving ramipril compared to 10% of controls reached the primary end points (significant difference)	115
PEACE	8290 (lower-risk patients)	Trandolapril, 4 mg/day	4.8 yr	Death, nonfatal MI, revascularization	No difference in primary outcome (21.9% in trandolapril vs 22.5% in controls)	118
QUASAR	336 (stable angina)	Quinapril, 40–80 mg/day	16 wk	Several indexes to assess myocardial ischemia	Short-term ACE inhibition was not associated with significant effects on transient ischemia	119
PART-2	617	Ramipril (5–10 mg/day)	2–4 yr	Carotid atherosclerosis by B-mode ultrasound, LV mass	Common carotid artery wall thickness or plaque thickness was not changed (LV mass was reduced)	120
SCAT	460 (compared with simvastatin)	Enalapril, 2.5 mg/day	47.8 mo	Quantitative coronary angiographic measurements	Simvastatin significantly slowed coronary artery disease progression (1.7% diameter stenosis vs 3.8% in placebo group); enalapril was neutral	121

MI indicates myocardial infarction; LV, left ventricular.

icantly increased in these specimens and chymase-positive cells were mainly mast cells in the media and adventitia.[129] In a rabbit model for aneurysm formation (elastase perfusion), aortic wall ACE protein levels increased during aneurysm growth in time.[130]

In mice, infusion of Ang II induced aneurysm formation independent of blood pressure changes. This was shown in a hyperlipidemic setting (in $ApoE^{-/-}$ mice) and in wild-type C57BL6 mice, although aneurysm formation was smaller in the wild-type mice.[97,131,132] In this model, proteolytic processes are clearly involved because the broad-spectrum matrix metalloproteinase (MMP) inhibitor doxycycline reduced the severity of aneurysm formation.[133] Ang II–induced aneurysm formation also displayed characteristic inflammatory features, which fits with the role of Ang II in inflammatory processes as described above. These studies suggest that Ang II, partly because of its inflammatory effects, is an important initiator of aneurysm.

Ang II–induced aneurysm formation was dependent on the presence of the AT_{1a} receptor on bone marrow–derived cells,[111] although other studies using AT_1 receptor blockers did not show a protective effect on aneurysm formation.[134,135] Absence of the MCP receptor CCR2 on bone marrow–derived cells reduced the incidence of Ang II–induced aneurysm formation in $ApoE^{-/-}$ mice.[136] Also, a recent study by Thomas et al showed that NAD(P)H oxidase activity is involved in Ang II–induced aneurysm formation. Deletion of p47phox attenuated aneurysm formation and reduced influx of macrophages and MMP-2 activity, again showing the importance of transactivating downstream signaling events of the AT_1 receptor.[137]

ACE inhibition has been shown to be beneficial for both structural and functional properties of aortic aneurysms. In 2 rat models, ACE inhibitors suppressed the development of aortic aneurysms,[134,135] whereas in patients with an aneurysm, ACE inhibition was associated with decreased stiffness and greater collagen turnover, which was considered favorable as stiffness is regarded as a risk factor for adverse events.[138] In a recent population-based case/control study, ACE inhibition was shown to reduce the risk of rupture of abdominal aortic aneurysms. Other antihypertensive agents, such as β-blockers, calcium channel blockers, thiazide diuretic, and angiotensin receptor blockers did not have these protective effects.[139] Although the numbers of patients that used AT_1 receptor blockers in this trial ($n=132$ patients, 1% of the population) was too small to draw solid conclusions, the surprising lack of effect of AT_1 receptor blockers to reduce aneurysm formation was also seen in animal studies.[134,135] This would suggest that ACE inhibitors would (1) have a protective effect on aneurysm formation mediated by other AT receptor subtypes, although not all studies confirm this; (2) have influenced the production of other RAS peptides; or (3) have reduced bradykinin degradation. Experimental or clinical studies supporting these mechanisms, however, are lacking.

Another mechanism to consider is the potential of ACE inhibitors to inhibit proteinases involved in extracellular matrix degradation, such as MMPs. The biological mechanism underlying this effect is that ACE inhibitors distinctively bind zinc, which is a cofactor for a number of MMPs.

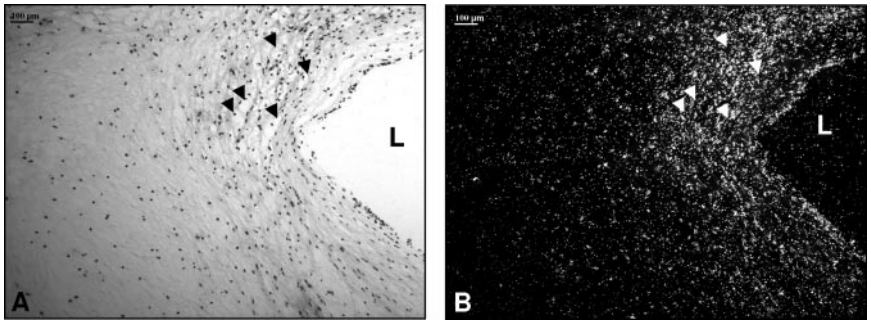

Figure 3. Cellular localization of ACE2 mRNA and protein in a human carotid artery with an advanced atherosclerotic lesion. A, An advanced carotid lesion was hybridized with an ACE2-specific riboprobe to detect mRNA using in situ hybridization, as shown in the dark field image of the same section in B. ACE2 mRNA is represented by a white signal. ACE2 mRNA was observed surrounding the core and in the shoulder regions of advanced atherosclerosis. Endothelial cells, SMCs, and macrophage foam cells expressed ACE2 mRNA.

Indeed, several studies have shown that ACE inhibitors specifically protect against rupture of the internal elastica lamina in vivo,[104,140] increased collagen type III synthesis in patients with aneurysm (assessed by circulating levels of propeptide of type III procollagen),[141] and reduced MMP-2 and MMP-3 gene and protein expression in human SMC cultures in vitro.[142] Thus, the capability of ACE inhibitors to directly inhibit MMPs could have an important role in their therapeutic effect during aneurysm formation.

Angiotensin-Converting Enzyme 2

ACE2 is a recently discovered homolog of ACE,[143–145] with a different catalytic profile. Data thus far suggest that ACE2 may act as a tissue-specific negative feedback regulator of the activated RAS.[146] Ang II serves as a substrate for ACE2 to generate Ang(1–7), and Ang I is an ACE2 substrate to generate Ang(1–9).[147] The function of Ang(1–9) is not yet well defined. Ang(1–7) may induce vasodilation and growth arrest (other substrates of ACE2 in Table 1). ACE2 may antagonize the actions of the ACE-Ang II axis, through both RAS-dependent and -independent effects. ACE2 itself may be antagonized by Ang II via a negative feedback loop of Ang II on ACE2 expression and activity.[148]

ACE2 and Vascular Remodeling

Although ACE2 activity has not yet been determined in the vascular wall, both protein and mRNA are expressed in human coronary arteries and arterioles and the vasa vasorum of most organs.[144,149] Recently, expression has also been shown in the large conduit arteries, ie, in the aorta and carotid of SHRs.[150] ACE2 localizes preferentially to endothelial cells and arterial SMCs.[144,149]

As for the role of ACE2 in vascular remodeling, the effect of ACE2 on neointima formation has not yet been studied, but Ang(1–7) infusion after balloon-catheter injury of the rat carotid artery reduced neointima formation.[151] This effect was probably mediated by its inhibition of vascular SMC proliferation.[152] In hypertensive animal models, ACE2 mRNA and protein were associated with immunoreactive Ang(1–7) in the large conduit arteries of SHRs. Treatment with an AT_1 receptor blocker induced a fivefold increase in ACE2 mRNA and was associated with a significant increase in aortic Ang(1–7) protein expression. This effect was associated with a decrease in aortic medial thickness, suggesting that this may be a protective mechanism in the prevention of cardiovascular events during hypertension.[150]

ACE2 and Atherosclerosis

Studies on the expression and activity of ACE2 in atherosclerosis are limited. Zulli et al showed the expression of ACE2 in endothelial cells, macrophages, and SMCs of aortic atherosclerosis in hypercholesterolemic rabbits.[153] No data on ACE2 activity in the lesions were presented. Notably, ACE2 was not expressed in endothelial cells of nondiseased thoracic aorta.

Recently, we have shown the presence of ACE2 mRNA (Figure 3) and its activity in human carotid atherosclerosis. ACE2 mRNA was present in all lesion types (early, advanced stable lesion, and lesions containing a thrombus). ACE2 protein was enzymatically active and lower in the stable advanced atherosclerotic lesions, compared with early lesions and lesions containing a thrombus. This suggests differential regulation of the ACE-ACE2 balance during progression of advanced to ruptured lesions (Sluimer et al[154] and SH, JS, MJAPD, JM Gase, A Michaud and P Corvol, unpublished observations, 2007).

Conclusion

Since its discovery, the RAS has evolved from a "simple" circulating hormonal system to a multifunctional system in which the traditional vasoactive role of Ang II is complemented with a plethora of other functions, such as oxidant stress and inflammatory and prothrombotic effects. Both experimental and clinical studies have shown the role of ACE and ACE generated proteins in vascular remodeling during restenosis, hypertension, atherosclerosis, and aneurysm formation. In experimental models of restenosis, hypertension, atherosclerosis, and aneurysm formation, ACE inhibition is generally effective in reversing vascular remodeling. Surprisingly, clinical trials, however, have not always confirmed these beneficial effects (see Figure 4). This discrepancy with the overall positive effects of experimental studies in which ACE inhibition proved to affect vascular remodeling is most likely related to the use of animal models. Apparently, the complex nature of the disease is not fully represented in these models, and it is likely that therapeutic intervention in a single pathway is not sufficient to reduce the clinical manifestations in patients. Clearly, more research is needed here, including the development of animal models that represent end-stage human disease.

For restenosis, ACE inhibition is not effective in reducing adverse events in patients following PTCA, and it is not likely that ACE inhibitors will be a therapeutic modality in restenosis. Several trials using ACE inhibition in patients with atherosclerosis and preserved cardiac function have been

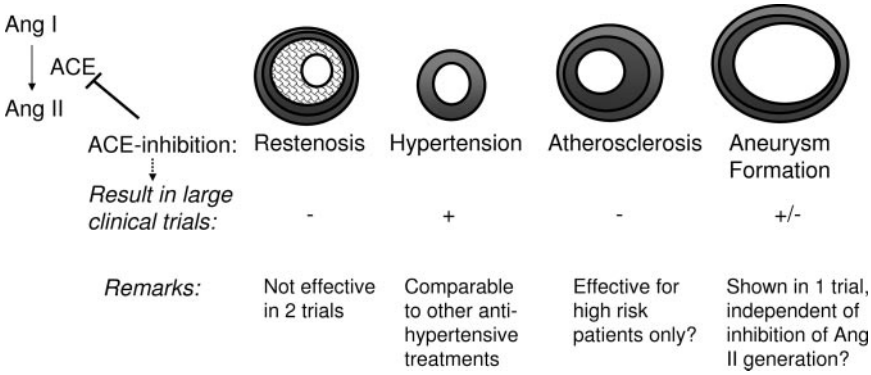

Figure 4. Diagram summarizing the effects of ACE inhibition during restenosis, hypertension, atherosclerosis, and aneurysm formation, as established in large clinical trials.

conducted; however, not all trials show beneficial effects on prevention of cardiovascular events. This questions the therapeutic potential of ACE inhibitors in these patients. It is thought that ACE inhibitors may be beneficial for patients with more risk factors but offer modest (to no) extra benefit for patients with low-risk factors or those who are already receiving treatment with statins and antiplatelet drugs. For aneurysm formation, there is 1 clinical trial that suggests that ACE inhibition reduces the risk of rupture of abdominal aortic aneurysms; thus, ACE inhibitors could be a therapeutic option; however, a direct effect of ACE inhibitors on MMP inhibition has to be considered as part of the working mechanism, and this needs to be further explored.

The impact of non–ACE-dependent Ang II generation by chymase is likely to be heterogeneous as expression and activity of chymase is highly species and vessel dependent. ACE2 is a recently discovered homologue of ACE, generating active peptide, such as Ang(1–7), and participating in the complex network and feedback mechanisms of the RAS. The role of ACE2 in vascular remodeling has yet to be established; however, ACE2 has been shown to be associated with vascular changes in hypertension and atherosclerosis. It is anticipated that ACE2 is important in the regulatory feedback mechanisms that control the RAS; however, more studies are needed to assess the exact role of ACE2 in various vascular pathologies.

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Disclosures

None.

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