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Role of the Renin–Angiotensin System in the Pathogenesis of Intimal Hyperplasia: Therapeutic Potential for Prevention of Vein Graft Failure?

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Abstract

The saphenous vein remains the most widely used conduit for peripheral and coronary revascularization despite a high rate of vein graft failure. The most common cause of vein graft failure is intimal hyperplasia. No agents have been proven to be successful for the prevention of intimal hyperplasia in human subjects. The rennin–angiotensin system is essential in the regulation of vascular tone and blood pressure in physiologic conditions. However, this system mediates cardiovascular remodeling in pathophysiologic states. Angiotensin II is becoming increasingly recognized as a potential mediator of intimal hyperplasia. Drugs modulating the renin–angiotensin system include angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. These drugs are powerful inhibitors of atherosclerosis and cardiovascular remodeling, and they are first-line agents for management of several medical conditions based on class I evidence that they delay progression of cardiovascular disease and improve survival. Several experimental models have demonstrated that these agents are capable of inhibiting intimal hyperplasia. However, there are no data supporting their role in prevention of intimal hyperplasia in patients with vein grafts. This review summarizes the physiology of the rennin–angiotensin system, the role of angiotensin II in the pathogenesis of cardiovascular remodeling, the medical indications for these agents, and the experimental data supporting an important role of the rennin–angiotensin system in the pathogenesis of intimal hyperplasia.

Introduction

Approximately 1,000,000 aortocoronary (coronary artery bypass grafting [CABG]) and peripheral vascular bypass procedures are performed each year using saphenous vein

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conduits. The leading cause of vein graft failure is intimal hyperplasia,¹ which leads to pathologic narrowing of the vessel lumen, graft stenosis, and ultimately graft failure.² Intimal hyperplasia is an unfortunate and nearly universal phenomenon occurring in the vein graft. It is an unsolved problem contributing to a substantial morbidity and cost, and remains the leading cause of vein graft failure in the short- (30 days to 2 years) and long-term (>2 years).³ The rate of vein graft failure among patients undergoing infrainguinal bypass ranges from 30% to 45% at 4 to 12 months postoperatively.⁴ The rate of per-patient vein graft failure 12 to 18 months after CABG was 45% among 1,920 patients in the Prevention of Vein Graft Failure Following Coronary Artery Bypass Graft Surgery (PREVENT) IV trial.⁵

Although the inciting mechanisms are not completely understood, intimal hyperplasia results from a cascade of molecular and cellular events. These include dedifferentiation of smooth muscles from a contractile to a secretory phenotype, with subsequent smooth-muscle cell proliferation and migration from the media to the intima, and extracellular matrix production and deposition.^{6,7} It has been demonstrated that 50% of intimal hyperplastic lesions leading to vein graft failure lie in the perianastomotic areas of the vein graft.⁸ The robust occurrence of intimal hyperplasia near anastomotic areas of the graft, and therefore near areas of vascular injury, suggests that intimal hyperplasia may represent a response to the injury that occurs during surgical harvest, the degree of which may be proportional to the degree of injury.⁹ Vascular remodeling in these regions is further exacerbated by hemodynamic alterations caused by systemic arterial pressures and changes in shear and laminar flow.³

Unfortunately, there are no therapeutic approaches that have demonstrated efficacy in reducing intimal hyperplasia in humans. There is a relative paucity of data regarding the pharmacologic management of patients after revascularization. Postoperative aspirin use improves graft patency by preventing thrombotic complications after revascularization, and its use is supported by consensus guidelines for patients undergoing lower-extremity bypass using vein grafts as well as angioplasty.^{10–15} The conflicting literature addressing the utility of other pharmacologic agents has focused mainly on statins, β -blockers, other antiplatelet agents, and anticoagulants. The pharmacologic management of peripheral arterial disease (PAD) is more clearly defined in the literature and is supported by several independent compilations of treatment guidelines,^{14–16} although data in this area remain in development. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) have received relatively little attention as potential agents to prevent vein graft failure after revascularization. However, these agents confer significant cardiovascular and survival benefits in populations with cardiovascular risk factors, including asymptomatic and symptomatic PAD, and their use in these patients is supported by two independent compilations of treatment guidelines.^{14,16} Conversely, the application of ACE inhibitors and ARBs for prevention of graft failure after revascularization is hampered by a lack of robust data in humans.

ACE inhibitors and ARBs are currently indicated for medical management of hypertension and in patients with cardiovascular risk factors, diabetes, diabetic nephropathy, or a history of stroke, myocardial infarction, or congestive heart failure.¹⁷ These agents inhibit cardiovascular remodeling and fibrosis in a variety of pathologic states. However, it is not known whether these agents prevent restenosis or intimal hyperplasia. There is a growing

body of literature demonstrating effectiveness of these agents in preventing both restenosis and intimal hyperplasia in vitro in human and animal tissue, and similar effects have also been demonstrated in vivo in several animal models. To date, no clinical trial has addressed the efficacy of these agents in preventing intimal hyperplasia in vein bypass grafts in humans. Thus, we present a review of the literature addressing the important role of angiotensin II in response to vascular injury and the pathophysiology of intimal hyperplasia. Additionally, we summarize the experimental data that support the therapeutic application of ACE inhibitors and ARBs in prevention of vein graft intimal hyperplasia.

Physiology of ACE, Angiotensin II, and the Renin–Angiotensin System

The rennin–angiotensin system is integral in the maintenance of cardiovascular homeostasis (Fig. 1). Under normal circumstances, renin acts on angiotensinogen to produce angiotensin I.¹⁸ ACE converts angiotensin I to angiotensin II. Angiotensin II is an octapeptide hormone that exerts its primary effects by binding to the AT₁ subtype of the angiotensin II receptor (AT₁R). ACE also acts as a kininase to hydrolyze circulating bradykinin to inactive peptides.^{19,20} Bradykinin acts on the B₂ receptor in the endothelium to stimulate production of nitric oxide (NO), prostacyclin, and endothelium-derived hyperpolarizing factor, resulting in vasodilation.^{20–22} Angiotensin II plays a central role in the regulation of blood pressure, circulating volume, and electrolyte balance. Its effects are both immediate (vasoconstriction) and delayed (aldosterone production and release; pituitary release of vasopressin, oxytocin, and adrenocorticotrophic hormone; stimulation of vascular smooth-muscle growth; and regulation of thirst).^{23,24}

ACE exists in two forms: a plasma protein and a membrane-bound ectoenzyme (tissue ACE) localized in several tissues.²⁵ Consequently, the rennin–angiotensin system is a complex system characterized by endocrine actions mediated by circulating plasma ACE as well as autocrine–paracrine actions mediated by tissue ACE. Tissue ACE has been recognized in multiple tissue types, including the kidneys, heart, brain, adrenal glands, and blood vessels. Tissue ACE is distributed throughout the arterial and venous endothelium, and angiotensin receptors are found throughout the vascular tree in endothelial as well as smooth-muscle cells.¹⁸ In contrast, renin is very limited in its tissue expression, but does exist in the tunica media of arterial and venous tissues.²⁶ The traditional view of this system holds that the conversion of angiotensin I to angiotensin II occurs by ACE, primarily in the pulmonary vascular bed.²⁷ However, it is now known that tissue ACE distributed systemically is the primary mediator of this conversion, as knockout of the tissue ACE mimics knockout of the entire enzyme in a mouse model.²⁸

Angiotensin II receptors exist in two subtypes: AT₁ and AT₂. Angiotensin II acts primarily through the AT₁ angiotensin II receptor (AT₁R) to exert the majority of its biologic effects. The AT₁R is expressed in vascular smooth muscle, heart, lungs, liver, kidney, brain, and adrenal glands.²⁹ In vascular smooth muscles, stimulation of the AT₁R mediates vasoconstriction, extracellular matrix formation, cell proliferation, inflammatory response, and oxidative stress.^{30,31} The AT₁R is a G-protein–coupled receptor, which activates several intracellular signaling pathways involving phospholipases A₂, C, and D, adenylate cyclase, voltage-dependent Ca²⁺ channels, several kinases involved in phosphorylation cascades

such as the *src* kinase–Ras–mitogen-activated protein kinase pathway,^{32–35} as well as nuclear factor- κ B.³⁶ In contrast, the AT₂ angiotensin II receptor (AT₂R) has limited tissue expression, and is restricted primarily to the brain and adrenal gland in adults.³⁷ However, the AT₂R becomes favored or upregulated in certain pathologic states^{38,39} and in states of pharmacologic AT₁R blockade.^{40,41} This receptor subtype mediates effects opposing that of the AT₁R, namely vasodilation and inhibition of vascular smooth-muscle growth.^{30,42}

Additional routes for angiotensin II production exist. Several other enzymes convert angiotensinogen or angiotensin I to angiotensin II in small quantities (e.g., chymase, chymostatin-sensitive ACE, cathepsin G, tissue plasminogen activator, elastase, and tonin; Fig. 1).²³ Of these, the most important is the serine protease chymase, which exists in many tissues, including vascular tissue.⁴³ However, ACE is the most important route for angiotensin II production, as its inhibition results in >90% reduction of angiotensin II formation.⁴⁴

Pharmacology of ACE Inhibitors and ARBs

ACE inhibitors block the circulating and tissue forms of ACE, preventing the conversion of angiotensin I to angiotensin II. In addition, ACE inhibitors block the kininase activity of this enzyme, leading to increased bradykinin levels. Increased bradykinin levels resulting from ACE inhibitor administration account for many of its adverse effects.⁴⁵ ARBs are highly selective antagonists of the AT₁R. These agents were developed to offer another option for inhibition of the rennin–angiotensin system. Because these drugs act by inhibiting the interaction between angiotensin II and the AT₁R, they do not lead to increased bradykinin levels, and therefore have an improved side-effect profile.

Medical Indications for ACE Inhibitors and ARBs

ACE inhibitors and ARBs are commonly used for management of a variety of medical conditions (Table I; please note this is meant as only a summary. The detailed review of the medical indications of ACE inhibitors and ARBs is beyond the scope of this work). These agents are effective in the management of hypertension.⁵⁸ The Joint National Committee in Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends ACE inhibitor or ARB therapy as the first-line management for patients with stage I hypertension with a history of diabetes, chronic kidney disease, stroke, myocardial infarction, or in patients at a high cardiovascular risk.¹⁷ ACE inhibitors and ARBs confer significant benefits in select patient populations. ACE inhibitors reduce the risk of myocardial infarction in patients with low ejection fractions,⁴⁷ prevent left ventricular remodeling after myocardial infarction,⁵⁰ reduce mortality after myocardial infarction in patients with heart failure,⁵¹ reduce mortality in patients with severe heart failure and reduced left ventricular ejection fraction,^{48,49} and delay progression of kidney disease in diabetic and nondiabetic patients.^{52–55} The American Diabetes Association recommends ACE inhibitor or ARB therapy for the management of hypertension or diabetic nephropathy in diabetic patients.⁵⁶ Similarly, the Kidney Disease Outcome Quality Initiative guidelines recommend ACE inhibitor or ARB administration in patients with nephrotic syndrome with or without diabetes.⁵⁷

Indications for ACE Inhibitor and ARB Use in Patients with PAD

There are no existing clinical guidelines to direct the global pharmacologic management of PAD after revascularization. Existing guidelines recommend using only antiplatelet agents.^{14,15} Instead, vascular practitioners are forced to rely on clinical guidelines for the management of PAD to direct medical management in this patient population.

Regarding ACE inhibitor and ARB use in PAD, existing evidence-based clinical guidelines come primarily from the findings in the Heart Outcomes Prevention Evaluation Study Investigators (HOPE) trial. In a subgroup of 4,051 patients with PAD in the HOPE trial, ACE inhibitor use conferred a 25% relative risk reduction in cardiovascular morbidity and mortality.⁴⁶ A follow-up study of the participants in the HOPE trial demonstrated that ramipril significantly reduced cardiovascular events and all-cause mortality in the subgroup of patients with clinical or subclinical PAD.⁵⁹ Moreover, an observational cohort study of 2,420 patients with PAD demonstrated a significant reduction in long-term mortality in patients taking ACE inhibitors.⁶⁰

Existing recommendations for the medical management of patients with lower-extremity PAD come from the American College of Cardiology/American Heart Association (ACC/AHA) 2005 guidelines (Table II). These contain a class IIa recommendation for ACE inhibitor use in patients with symptomatic PAD to reduce the risk of cardiovascular events based on level B evidence.¹⁶ A 2006 update of the ACC/AHA guidelines offers a class I recommendation based on level A evidence for use of ACE inhibitors in all patients with a left ventricular ejection fraction $\geq 40\%$ and in all patients with hypertension (blood pressure $\geq 140/90$ mm Hg or $\geq 130/80$ mm Hg in patients with chronic kidney disease or diabetes), diabetes, or chronic kidney disease, unless contraindicated; ARBs are recommended for use in patients who are intolerant of ACE inhibitors.⁶¹ The Inter-Society Consensus for the Management of Peripheral Arterial Disease (II) guidelines recommend consideration of ACE inhibitors as an initial agent for the management of hypertension in patients with PAD to reduce the risks of cardiovascular events.¹⁴ Therefore, applying these guidelines, an ACE inhibitor or ARB should be considered as part of the medical management strategy in patients undergoing revascularization, particularly in patients with hypertension, heart failure (left ventricular ejection fraction $\geq 40\%$), diabetes, or chronic kidney disease.

Suboptimal Use of Cardioprotective Medications in Patients Undergoing Revascularization

According to current literature, ACE inhibitors and ARBs are underutilized in patients with PAD, both before and after revascularization. A prospective study of patients with PAD referred to a vascular clinic for surgical evaluation demonstrated ACE inhibitor use in only 55% of patients, despite an 81% prevalence of hypertension and a 55% prevalence of diabetes mellitus.⁶² Accordingly, in this cohort, the antihypertensive regimens of 29% of patients were found to be noncompliant with the ACC/AHA 2005 guidelines. A single-institution prospective cohort study of patients undergoing peripheral vascular interventions observed ACE inhibitor use in only 42% of patients at hospital discharge, and this declined to 36% at 6 months, despite a 92% prevalence of hypertension, a 23% prevalence of

diabetes, and a 23% prevalence of heart failure.⁶³ A retrospective study examining the perioperative pharmacologic regimen in patients undergoing infrainguinal revascularization noted ACE inhibitor use in only 50% of patients undergoing infrainguinal revascularization, despite a 70% prevalence of hypertension, 53% prevalence of diabetes mellitus, and 14% prevalence of congestive heart failure.⁶⁴ There is a growing consensus in the vascular literature that vascular surgeons should be more involved in the pharmacologic management of these patients, and should redirect therapy toward evidence-based guidelines when necessary.^{62,65,66}

Role of the Renin–Angiotensin System in the Pathophysiology of Intimal Hyperplasia

In a variety of pathologic states, including vascular injury, hypertension, atherosclerosis, and myocardial infarction, the rennin–angiotensin system is a powerful mediator of cardiovascular dysfunction and remodeling (Fig. 2). Cardiovascular remodeling is a maladaptive process leading to vascular and myocardial hypertrophy and myocardial fibrosis. In response to chronic alterations in mechanical forces and variations in flow, such as in systemic hypertension, morphological alterations in the vascular tissue and myocardium are mediated by angiotensin II.^{23,67} Vascular remodeling represents the culmination of several deleterious events, including smooth-muscle cell hyperplasia and extracellular matrix production.²³

Revascularization procedures cause varying amounts of unavoidable injury and trauma to the vascular wall. Injury varies from damage restricted to the vascular endothelium, to full-thickness injury to the vascular wall, depending on the intervention performed. Several key enzymes in the tissue rennin–angiotensin pathway are expressed in response to vascular injury, effectively poisoning the vascular tissue to both produce and to respond vigorously to angiotensin II. Vascular stretch stimulates release of angiotensin II.^{68,69} Vascular injury induces expression of tissue ACE⁷⁰ and angiotensinogen in the media and neointima.⁷¹ Moreover, the AT₁R—the principle receptor responsible for the physiologic as well as the pathophysiologic effects of angiotensin II—is expressed at increased levels in the intima in response to vascular injury.⁷²

The endothelium is vital in regulating vascular homeostasis via its influence on thrombosis, proliferative responses, inflammation, and vascular tone. Endothelial dysfunction resulting from denudation, damage, or biochemical perturbation has been implicated as an important step in the cascade, leading to intimal hyperplasia.⁷³ Angiotensin II contributes to endothelial dysfunction via several mechanisms. In pathologic states such as hypertension, heart failure, or atherosclerosis, angiotensin II exerts proapoptotic, prothrombotic, proinflammatory, and prooxidant effects.^{31,67,74} Through its actions on the AT₁R, angiotensin II stimulates production of vascular NADPH oxidase and formation of superoxide radicals.^{75–77} Vascular stretch that accompanies vascular injury and hypertension further exacerbates vascular production of reactive oxygen species and causes NO depletion.⁴² Angiotensin II favors a prothrombotic environment by activation of plasminogen activator inhibitor-1 and tissue factor.^{78–80} Angiotensin II also initiates a proinflammatory response by inducing expression of vascular cell adhesion molecule-1 and

intercellular adhesion molecule-1 on vascular smooth-muscle cells (VSMCs), tumor necrosis factor- α , interleukin-6, and the chemoattractant protein monocyte chemotactic protein-1, in a manner similar to that observed in diabetes and atherosclerosis.^{81–85} As a consequence, angiotensin II promotes endothelial dysfunction. It also triggers vascular endothelial apoptosis via activation of caspase-3.⁸⁶ As will be explained later, pharmacologic inhibition of angiotensin II production improves endothelial function.

Smooth-muscle cell proliferation and migration are key events contributing to intimal hyperplasia, and the VSMC is the principal cell type in the hyperplastic lesion.⁸⁷ Angiotensin II is a mediator of VSMC growth and proliferation. Administration of angiotensin II stimulates VSMC growth in vitro in cell culture models of rat aortic smooth muscle⁸⁸ and human aortic smooth muscle.⁸⁹ Furthermore, in vivo experiments using a rat model of carotid balloon injury have demonstrated that administration of angiotensin II induces smooth-muscle cell DNA synthesis and proliferation at the site of vascular injury.⁹⁰ Angiotensin II promotes both hypertrophy⁸⁸ and hyperplasia^{89,90} of VSMCs. Importantly, angiotensin II induces VSMC replication independent of its effects on blood pressure.⁹¹

Vascular smooth-muscle growth is regulated by proliferative and antiproliferative pathways involving platelet-derived growth factors, fibroblast growth factors, and transforming growth factors. These growth factors mediate proliferative and antiproliferative effects that achieve a homeostatic balance in physiologic states. In states of vascular stress, such as atherosclerosis or vascular injury, VSMCs undergo rapid proliferation and migration. Angiotensin II augments this process in states of injury by disrupting the balance between proliferative and antiproliferative pathways mediating VSMC growth.^{92,93} By activating platelet-derived growth factors, basic fibroblast growth factors, and transforming growth factor- β (autocrine growth factors), angiotensin II stimulates dual proliferative and antiproliferative loops in vascular smooth muscle, the end result being VSMC hypertrophy and/or hyperplasia.^{92–94} Additionally, angiotensin II stimulates matrix metalloproteinase production,⁹⁵ which is a key step in VSMC proliferation and migration, and ultimately many components of stenosis and remodeling.^{96,97}

Renin–Angiotensin Inhibition Prevents Endothelial Dysfunction

Several studies have examined the effects of rennin–angiotensin inhibition on endothelial function. ACE inhibitors prevent endothelial dysfunction in human saphenous veins (HSVs) in vitro. Ko et al. measured isometric tension and endothelial-dependent relaxation in HSV segments procured at the time of CABG. HSV segments from patients who were taking preoperative ACE inhibitors demonstrated significantly enhanced endothelial-dependent relaxation in comparison with those from patients who were not taking ACE inhibitors.⁹⁸ Both ACE inhibitors and ARBs have been demonstrated to preserve endothelial function in vivo in several animal models. Endothelial NO synthase (eNOS) activity is preserved after chronic systemic therapy in normotensive rats.⁹⁹ Ramipril preserves endothelial function in aortic segments from rabbits fed an atherogenic diet.^{100,101} Cilazapril prevents hypertension-induced endothelial dysfunction in hypertensive rats, presumably through a mechanism relating to bradykinin balance, NO release, or regulation of prostaglandin release.¹⁰² Moreover, ACE inhibitors prevent vascular endothelial apoptosis in a rat

model.¹⁰³ ACE inhibitors quinapril and quinaprilat and the ARB losartan improve endothelial function in human subjects as measured by flow-mediated vasodilation of the brachial artery.^{20,22,104} Moreover, coronary endothelial-derived vasorelaxation is improved in patients taking quinapril.¹⁰⁵

ACE inhibitors and ARBs exert multiple protective effects on the vascular endothelium, which collectively enhance endothelial function. A major benefit of these agents is in blocking the activation of the NADPH oxidases by endogenously produced angiotensin II. The activity of these enzymes is increased in virtually all diseases in which angiotensin II is increased, including vascular injury, hypertension, atherosclerosis, and diabetes. In response to vascular injury or in pathologic states such as hypertension, angiotensin II promotes oxidative stress⁴² and vascular endothelial dysfunction and apoptosis.^{86,106} NADPH oxidases represent one of the most important sources for superoxide production, and angiotensin II is the most important source for the activation of the NADPH oxidases.¹⁰⁷ Reactive oxygen species produced by the NADPH oxidases not only inactivate NO via radical-radical reactions but also directly alter the eNOS enzyme and oxidize the eNOS cofactor tetrahydrobiopterin.^{42,108–110} Moreover, ACE inhibitors containing a sulfhydryl group may have direct antioxidant effects relating to this side group.¹¹¹

Because ACE is a kininase that inactivates bradykinin, inhibition of ACE therefore increases the circulating levels of this compound. Bradykinin is a potent vasodilator that acts through B2 receptors on vascular endothelium to stimulate NO production, prostacyclin, and endothelium-derived hyperpolarizing factor.^{20–22}

ACE inhibitors and ARBs also have anti-inflammatory effects. By reducing the expression of adhesion molecules on vascular endothelium, these agents can prevent the entry of leukocytes into the vessel wall, and reduce the vascular levels of cytokines that further stimulate NADPH oxidase activation and reduce eNOS function.^{112–114} Moreover, expression of adhesion molecules is inhibited by NO and favored by angiotensin II.^{85,115} Actions of angiotensin II on the AT₂R, which are favored by AT₁R blockade, can also enhance NO production, as the AT₂R mediates effects opposing those of the AT₁R, including vasodilation.^{40,41} As a cumulative result of these factors, angiotensin II blockade improves endothelial function.

Animal Data Demonstrating a Reduction in Intimal Hyperplasia by Treatment with ACE Inhibitors and ARBs

ACE inhibitors and ARBs have been demonstrated to prevent intimal hyperplasia in several in vitro model systems using human and animal tissues, and in several animal models of restenosis and intimal hyperplasia (Table III). Owens was the first investigator to demonstrate the growth-preventing effects of ACE inhibitors in vascular tissue.¹¹⁷ He administered the ACE inhibitor captopril, the vasodilator hydralazine, or the β -blocker propranolol to spontaneously hypertensive rats. A significant reduction in smooth-muscle cell proliferation and medial hypertrophy was observed in the group treated with ACE inhibitor. Moreover, the growth-inhibiting effects of captopril were independent of its blood pressure-lowering effects, as hydralazine and propranolol failed to inhibit medial thickening

to the same degree. Subsequent to this, ACE inhibitors have been demonstrated to inhibit intimal hyperplasia in a rat model of carotid balloon injury,¹¹⁸ a dog model of common carotid bypass using external jugular vein,¹¹⁹ and a rabbit model of common carotid interposition with external jugular vein.¹²⁰ However, the use of ACE inhibitors did not inhibit intimal hyperplasia in a baboon model of vascular injury.¹²⁴ ARBs have been demonstrated to inhibit intimal hyperplasia in organ culture of HSV,¹¹⁶ a rabbit model of common carotid interposition with external jugular vein,^{121,122} and a canine model of common carotid interposition with external jugular vein.¹²³

With the exception of the baboon model, administration of ACE inhibitors and ARBs has demonstrated efficacy in inhibiting intimal hyperplasia in every animal model studied to date. Whether this lack of a significant effect was due to the small sample size, the choice of ACE inhibitor and the dose used, or an important difference in the biology of the rennin–angiotensin system of primates is unclear. Can these differences be accounted for by interspecies variation in tissue penetration, drug metabolism, bioavailability, and clearance? Does the choice of ACE inhibitor matter? In addition, is there an interspecies difference in the dose required for adequate inhibition of tissue ACE? It should be noted that adequate inhibition of tissue ACE may require higher or even maximal dosing of ACE inhibitors; even at maximal ACE inhibitor doses, angiotensin II is still detectable.¹²⁵

Human Studies Examining the Effect of ACE Inhibitors after Revascularization

Prospective data regarding the influence of rennin–angiotensin inhibition on outcomes after revascularization are limited to two trials investigating the ACE inhibitor cilazapril in patients undergoing coronary arterial balloon injury; ARBs have not been investigated prospectively in human subjects. After demonstration of the success of cilazapril in preventing myointimal proliferation after balloon injury in rat carotid artery,¹¹⁸ two human trials were conducted to investigate the effect of this agent in patients undergoing percutaneous transluminal coronary angioplasty (PTCA). The first of these trials, named the Multicenter European Research Trial With Cilazapril After Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis (MERCATOR), investigated the benefit of cilazapril in prevention of restenosis after PTCA.¹²⁶ This trial was randomized, double-blinded, and placebo-controlled. Subjects were randomized to cilazapril or placebo beginning in the evening after successful PTCA, and the medication was continued for 6 months at which time patients underwent repeat coronary angiography. The trial failed to show a difference in the coronary artery lumen diameter at 6-month follow-up angiography in the cilazapril group.

The second human trial, named the Multicenter American Research Trial With Cilazapril After Angioplasty to Prevent Transluminal Coronary Obstruction and Restenosis (MARCATOR),¹²⁷ designed to test the effect of cilazapril on restenosis after PTCA was of a similar nature and was conducted in America. This trial was also randomized, double-blinded, and placebo-controlled. The trial was designed to assess the influence of low-, intermediate-, and high-dose cilazapril on subsequent development of angiographic

restenosis. The trial also failed to show a significant difference in the coronary artery lumen diameter at 6-month follow-up angiography in the patients taking cilazapril.

Although these trials failed to demonstrate a benefit of ACE inhibitors in prevention of restenosis, these results cannot be extrapolated to patients undergoing vascular bypass with vein grafts, for several important reasons. First, arteries and veins have important anatomical, structural, and functional differences.^{3,128–130} In addition, the component of the rennin–angiotensin system mediated by tissue ACE differs in venous and arterial tissue. Arterial tissue has reduced tissue ACE activity compared with venous conduits.^{131,132} Borland et al. measured tissue ACE activity in various blood vessels and found 3-fold higher ACE activity in saphenous vein and 3.5-fold higher ACE activity in old saphenous vein conduits from explanted hearts compared with internal thoracic artery.¹³¹ Moreover, these properties were retained by the conduit up to 20 years after CABG. Yang et al. have additionally demonstrated that ACE inhibitors markedly augment endothelial-dependent relaxation to bradykinin in HSV, but not in internal mammary artery.¹³² These results suggest that venous bypass grafts may differ from balloon-injured arteries in their response to systemic treatment with ACE inhibitors.

There is a second important limitation of the MERCATOR and MARCATOR trials: ACE inhibitor therapy was not initiated until after the procedure. Every in vivo animal study demonstrating a reduction in intimal hyperplasia in experimental vein grafts with ACE inhibitor or ARB treatment has proven the importance of pretreatment before revascularization. In vivo animal studies demonstrated a reduction in intimal hyperplasia in experimental vein grafts by pretreating them with ACE inhibitor or ARB for 5 to 7 days before surgical bypass, allowing adequate systemic effects of the drug at the time of vascular injury.^{118–123}

Finally, the doses of ACE inhibitors used in the MERCATOR and MARCATOR trials may have been inadequate for inhibition of tissue ACE. The important role of tissue ACE in the rennin–angiotensin system has been well documented.^{18,24} An antihypertensive dose of ACE inhibitor was used in the MERCATOR and MARCATOR trials. Using a rat model of balloon injury to the carotid artery, Rakugi et al. demonstrated that conventional doses of the ACE inhibitor quinapril are adequate for antihypertensive effects and for inhibition of circulating ACE, whereas higher doses were needed to inhibit the activity of tissue ACE.²⁵ These findings create an added challenge in the pharmacologic management of intimal hyperplasia. The goal would be to achieve an ACE inhibitor dose high enough to inhibit tissue ACE, while preventing excessive ACE inhibitor dosing so as to avoid adverse effects. The optimum dosing requires further investigation.

Two prospective trials have examined the effect of treatment with an ACE inhibitor on ischemic complications after coronary revascularization. The Angiotensin-Converting Enzyme Inhibition Post Revascularization Study (APRES) randomized 159 patients with asymptomatic moderate left ventricular dysfunction undergoing CABG or PTCA to ramipril or placebo therapy beginning after revascularization and continuing for a median follow-up of 33 months.¹³³ The authors noted a significant reduction in the triple composite end point of cardiac death, acute myocardial infarction, or clinical heart failure, although graft patency

was not assessed. Similarly, the Effects of Quinapril on Clinical Outcome After Coronary Bypass Grafting Study (QUO VADIS) randomized 149 patients scheduled to undergo CABG to quinapril or placebo beginning 4 weeks preoperatively and continuing for 1 year.¹³⁴ Although the authors noted a significant reduction in the primary end point of clinical ischemic events, they did not note a reduction in ischemic events at exercise testing and Holter monitoring. Again, graft patency was not assessed.

A retrospective review of 293 patients who underwent infrainguinal bypass for PAD analyzed the use of cardioprotective medications before and after surgery, including ACE inhibitors, and investigated the subsequent influence on graft patency.⁶⁴ The authors correlated the use of ACE inhibitors, statins, antiplatelet agents, and warfarin with vein graft patency. Patients taking ACE inhibitors were grouped into two categories: those who were administered ACE inhibitors at any time pre-, peri-, or postoperatively; and those who were not taking these drugs. The authors did not observe a difference in graft patency between patients who were taking ACE inhibitors (either pre-, peri-, or postoperatively) and those who were not. However, the authors did observe an overall decrease in mortality in patients taking ACE inhibitors, consistent with the primary end point demonstrated in the subset of patients with PAD in the HOPE trial.⁴⁶

Discussion

Intimal hyperplasia remains a perplexing problem contributing to substantial morbidity, mortality, and cost after revascularization procedures. There is a significant and growing body of literature supporting the notion that pharmacologic inhibition of the rennin–angiotensin system attenuates intimal hyperplasia and enhances vascular endothelial function, either via blockade of production (by ACE inhibitors), or by antagonism at the AT₁R (by ARBs). Each of these agents plays a unique role in renin-angiotensin inhibition. ARBs provide a complete blockade of the AT₁R, preventing effects of both locally and systemically produced angiotensin II. Alternatively, ACE inhibitors cause a subtotal inhibition of angiotensin II production at both systemic and tissue levels. These effects are dose-dependent, with high doses required for adequate inhibition of tissue ACE. Additionally, these agents have the unique benefit of increasing bradykinin levels, thereby enhancing endothelial function. Existing evidence-based guidelines for medical management of PAD recommend ACE inhibitor use in patients with concurrent hypertension, diabetes, kidney disease, or heart failure based on the clear survival benefits incurred by these agents. Nevertheless, these drugs remain underutilized in the population with PAD, both before and after revascularization. Despite promising animal studies demonstrating a reduction in intimal hyperplasia with ACE inhibitor and ARB use in vein grafts, no human trials have examined the role of ACE inhibitors and/or ARBs in prevention of vein graft failure.

The inevitable vascular injury initiated by surgical vein harvest triggers a cascade of deleterious events contributing to intimal hyperplasia of the vein graft. Careful vein harvest and surgical preparation can only go so far in ameliorating perioperative vascular injury. Even with careful surgical technique and “no-touch” vein harvest, transmural vascular injury is unavoidable, particularly in the perianastomotic areas of the bypass conduit. Moreover, placement in systemic arterial circulation subjects the vein conduit to hemodynamic

alterations that promote maladaptive remodeling. If a strategy is to be successful in optimizing outcomes from bypass, it is sensible to target a central mediator of the downstream effects initiated by this unavoidable injury. In the case of vein graft bypass conduits, angiotensin II is a central mediator of oxidative stress, inflammation, endothelial dysfunction, smooth-muscle proliferation, and extracellular matrix deposition. Can we exploit the beneficial effects of ACE inhibitors and ARBs for prevention of intimal hyperplasia? Though pre-, peri-, and postoperative systemic administration of these agents has demonstrated efficacy in reduction of vein graft intimal hyperplasia in animal models, it is unknown whether these effects would be replicated in the heterogeneous human population undergoing revascularization. There are many potential avenues of investigation relating to the optimum form of drug delivery (systemic vs. local), dosage, and timing of delivery, as well as the possible benefit of combination therapy with ACE inhibitors and ARBs. If administration of these inexpensive and widely available agents to patients undergoing revascularization could help prolong bypass graft patency, this simple maneuver would improve patient outcomes and reduce the costs associated with bypass graft occlusion and failure.

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Fig. 1.

Schematic representation of the rennin–angiotensin system and its physiologic effects on vascular endothelium and vascular smooth muscle. ACE, angiotensin-converting enzyme; eNOS, endothelial nitric oxide synthase; VSMC, vascular smooth-muscle cell; ECM, extracellular matrix; EDHF, endothelium-derived hyperpolarizing factor.

Fig. 2.

Schematic representation demonstrating the role of the rennin–angiotensin system in the pathophysiology of intimal hyperplasia, highlighting the effects on vascular endothelium and vascular smooth muscle. Arrows (↑ and ↓) are placed to emphasize differences occurring with vascular injury relative to the physiologic state. ACE, angiotensin-converting enzyme; NO, nitric oxide; TNF, tumor necrotic factor; VCAM, vascular cell adhesion molecule; ICAM, intercellular adhesion molecule; IL, interleukin; MCP, monocyte chemotactic protein; VSMC, vascular smooth-muscle cell; ECM, extracellular matrix; MMP, matrix metalloproteinase.

Table I
Current medical indications for angiotensin-converting enzyme inhibitor and angiotensin receptor blocker use

Indication	Benefit
Hypertension with history of DM, CKD, stroke, or MI Patients with high cardiovascular risk	Reduction in the risks of death, stroke, MI, heart failure, cardiac arrest, progression to revascularization, and diabetic complications ^{17,46}
Left ventricular dysfunction	Reduction in risk of MI ⁴⁷
	Reduction in mortality ^{48,49}
After MI	Prevents left ventricular remodeling ⁵⁰
After MI with heart failure	Reduction in mortality ⁵¹
DM with hypertension or nephropathy	Delays diabetic nephropathy ⁵²⁻⁵⁶
Nephrotic syndrome with or without DM	Delays progression of CKD ⁵⁷

DM, diabetes mellitus; CKD, chronic kidney disease; MI, myocardial infarction.

Table II
Indications for ACE inhibitor and/or ARB therapy in patients with PAD

Indication	Agent	Source	Class of recommendation (level of evidence)	Benefit
Heart failure (LVEF 40%) in patients with any atherosclerotic vascular disease	ACE inhibitor or ARB	JNC-VII ¹⁷ ; AHA/ACC 2006 updated guidelines ⁶¹	I (A)	Reduction in cardiovascular remodeling, reduction in myocardial infarction, reduction in mortality
Diabetes mellitus in patients with any atherosclerotic vascular disease	ACE inhibitor or ARB	JNC-VII ¹⁷ ; AHA/ACC 2006 updated guidelines ⁶¹	I (A)	Reduction in the incidence of cardiovascular disease and stroke, delayed progression of diabetic nephropathy, and reduction in albuminuria
Chronic kidney disease in patients with any atherosclerotic vascular disease	ACE inhibitor or ARB	JNC-VII ¹⁷ ; AHA/ACC 2006 updated guidelines ⁶¹	I (A)	Delayed progression of diabetic and nondiabetic renal failure
Initial antihypertensive in patients with PAD	ACE inhibitor	TASC II guidelines ¹⁴	II (B)	Reduction in the risk of cardiovascular events
Lower-risk patients after revascularization with normal LVEF with well-controlled cardiovascular risk factors	ACE inhibitor	AHA/ACC 2006 updated guidelines ⁶¹	II (B)	Reduction in the risk of cardiovascular events

LVEF, left ventricular ejection fraction; PAD, peripheral arterial disease; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; JNC-VII, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; AHA/ACC 2006 updated guidelines, American Heart Association/American College of Cardiology Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update; TASC, Trans-Atlantic Inter-Society Consensus for the Management of Peripheral Arterial Disease.

Table III
In vitro and in vivo experimental models investigating the effects of angiotensin-converting enzyme inhibitors or ARBs on vascular proliferation and intimal hyperplasia

Author	Drug tested	Species	Model	Findings
Varty et al. ¹¹⁶	Losartan	Human	Organ culture of human saphenous vein	33% reduction in intimal thickness at 14 days in organ culture with losartan treatment
Owens ¹¹⁷	Captopril vs. hydralazine vs. propranolol	Rat	Reduction of aortic smooth-muscle cell hypertrophy and polyploidism in spontaneously hypertensive rats	Statistically significant reduction in medial smooth-muscle hypertrophy and polyploidism with captopril treatment vs. hydralazine and propranolol, independent of blood pressure-lowering effects
Powell et al. ¹¹⁸	Cilazapril initiated 6 days before injury	Rat	Balloon injury to common carotid artery of rats	80% reduction in intimal thickness at 14 days with cilazapril treatment
Flores et al. ¹¹⁹	Perindopril initiated 7 days preoperatively	Dog	External jugular vein to common carotid artery interposition	31.3% reduction in intimal/medial ratio at 1 week and a 53.4% reduction in intimal/medial ratio at 4 weeks with perindopril treatment
O'Donohoe et al. ¹²⁰	Captopril initiated 7 days preoperatively	Rabbit	External jugular vein to common carotid artery interposition	40% reduction in intimal thickness at 28 days with captopril treatment
Fulton et al. ¹²¹	Experimental ARB L158, 809 initiated 5 days preoperatively	Rabbit	External jugular vein to common carotid artery interposition	43% reduction in intimal thickness at 28 days with L158,809 treatment
Davies et al. ¹²²	Experimental ARB L158, 809 initiated 5 days preoperatively	Rabbit	External jugular vein to common carotid artery interposition	48% reduction in intimal thickness and a 45% reduction in medial thickness at 28 days with L158,809 treatment
Yuda et al. ¹²³	Experimental ARB L158, 809 initiated 7 days preoperatively	Dog	External jugular vein to common carotid artery interposition	79% reduction in intimal thickness and a 70% reduction in intimal/medial ratio at 28 days with L158,809 treatment
Hanson et al. ¹²⁴	Cilazapril initiated 7 days preoperatively	Baboon	Carotid endarterectomy, balloon injury of SFA, bilateral aortoiliac bypass using expanded PTFE	No difference in intimal or medial thickening in control and cilazapril-treated animals at 3 months

ARB, angiotensin receptor blocker; SFA, superficial femoral artery; PTFE, polytetrafluoroethylene.