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Carotid Artery Intima-Media Thickness and the Renin-Angiotensin System

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Abstract

Carotid artery intima-media thickness (IMT) is a biomarker for cardiovascular disease that also predicts the risk of cardiovascular mortality. Angiotensin-converting enzyme (ACE) inhibition is a unique therapeutic modality because it both treats hypertension and improves arterial health and cardiovascular disease outcomes. Controversy exists regarding the role of ACE inhibitors and angiotensin receptor blockers (ARBs) in IMT regression. Our article provides an update on how ACE inhibitors and ARBs could play a role in decreasing IMT.

Keywords

intima-media thickness; cardiovascular disease; renin-angiotensin system; angiotensin-converting enzyme inhibitor; angiotensin II receptor blockers

Introduction

Cardiovascular disease (CVD) is the leading cause of death in the United States.[1] Atherosclerosis is a major mediator of cardiovascular morbidity and mortality. The atherosclerotic process begins in youth and progresses with age.[2,3] Carotid intima-media thickness (IMT) has been shown to be a predictor of atherosclerosis and coronary heart disease.[4,5] The goal of IMT monitoring is to identify and treat at-risk patients before a cardiovascular event occurs and to use IMT regression as a biomarker to assess the effectiveness of medical therapy.

The progression of atherosclerotic disease occurs over time through diverse mechanisms. Hypertension and aging promote both arteriosclerosis and atherosclerosis, and it has been shown that inhibition of the renin-angiotensin system (RAS) improves outcomes in patients

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with CVD.[6] Mechanistically, activation of the RAS increases angiotensin I conversion to angiotensin II, leading to increased stimulation of the angiotensin II type 1 (AT1) receptor in the blood vessel wall. Signaling by the AT1 receptor increases oxidative stress and endothelial cell dysfunction by decreasing nitric oxide (NO) levels from reduced NO synthase (NOS) activity[7]; increasing nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity and expression[8]; reducing NO from interacting with superoxide to form peroxynitrite;[8] and increasing reactive oxygen species through the uncoupling of NO synthase and reducing levels of tetrahydrobiopterin (BH4).[8]

The resultant blood pressure elevation further increases local RAS activity, increasing IMT and wall stiffness through endothelial dysfunction.[9] This self-perpetuating loop eventually leads to symptomatic arterial disease or death. Blocking RAS activity by angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) theoretically breaks this loop. These agents promote vascular health by reducing blood pressure and end-organ damage,[10] reducing arterial stiffness,[11] and reversing endothelial dysfunction by increasing NO levels.[12,13]

Intima-media thickness can be measured in any artery, but the common carotid arteries and femoral arteries are most often used for measurment. These are superficial arteries that are usually well visualized by duplex ultrasound. The arterial wall furthest from the ultrasound transducer is measured.[14]

It has been shown that ultrasound IMT measurements correlate with histologic findings in addition to atherosclerotic disease.[15] B-mode and M-mode ultrasounds can be used to measure IMT. B-mode ultrasound is performed with the highest possible frequency to optimize resolution and produce a 2-dimensional image. M-mode ultrasound samples a single point in time and is used mainly in echocardiography. B-mode ultrasound is the standard technique used to image IMT because it is not limited to a discrete point and produces 2-dimensional images from which measurements can be taken.[16] Studies with B-mode ultrasound are easy to perform and widely available, but the accuracy of the results depends on the experience of the vascular laboratory.[17] Automatic border-detection software can be used to help standardize the IMT measurement protocol.[18] The common carotid artery is often used for IMT measurements because of its proximity to the skin and resistance to plaque development.[14,15] A specific protocol and interpretation method has not been agreed on; however, the Carotid Intima Media Thickness Task Force[19] has recommended several research protocols that have been applied in several large clinical studies and study data have provided consistent results. Subsequently, common carotid artery IMT has been validated as a biomarker for CVD in the literature.[5,20] The Framingham Heart Study correlated increased common carotid IMT and carotid plaques with a higher Framingham risk score. The study also postulated that IMT could discriminate between low and high 10-year CVD risk.[21] Increased IMT has been associated with increased risk for myocardial infarction and stroke.[5,18,22,23] Carotid IMT in childhood has been shown to predict cardiovascular risk later in life.[24] Microvascular diabetes complications have been shown to coincide with increased IMT.[25] Using IMT as a biomarker for CVD is posited to improve the rational stratification of at-risk patients and focus medical therapy to those patients who will benefit most. With the incidence of CVD rising and longevity increasing,

effectively assessing risk and preventing disease is a critical societal issue.[26] Inhibiting the RAS reduces cardiovascular morbidity and mortality, suggesting that IMT could be related to these observed effects.[2,27] This article summarizes the risk factors for IMT, the relationship between the RAS and IMT, and the current status of clinical trials evaluating the impact of the RAS on IMT regression.

Risk Factors for IMT Progression

Because IMT is a validated biomarker for CVD, it is not surprising that many of the risk factors identified for IMT progression parallel the risk factors for CVD. The main determinant of IMT is aging.[28] Men exhibit a more increased IMT and increased IMT progression rate than women.[29,30] Metabolic syndrome and its components also influence IMT.[31] Dysglycemia, hypertension, dyslipidemia, and obesity have been shown to increase IMT.[32–37] However, when presenting together, as in metabolic syndrome, their synergism augments IMT.[31,38] Smoking is another major risk factor that accelerates IMT progression.[39,40] Less common risk factors that increase IMT are radiation exposure and genetic polymorphisms.[41,42]

Medical Therapies That Improve IMT

It has been shown that IMT progression can be reduced by treating risk factors. Dyslipidemia and hypertension have been the most widely studied and treated disorders. Treatment with pravastatin improved dyslipidemia and reduced IMT progression in patients enrolled in the Regression Growth Evaluation Statin Study (REGRESS),[43] Pravastatin, Lipids, and Atherosclerosis in the Carotid Arteries (PLAC-II) study,[44] and the Kuopio Atherosclerosis Prevention Study (KAPS).[17] In addition to the effect of statin therapy on IMT, several other studies have indicated that treating hypertension with calcium channel blockers[45–47] and β-adrenergic receptor antagonists[48,49] also improves IMT. Calcium channel blockers may have a particular benefit in patients with type 2 diabetic mellitus who have concurrent hypertension,[50] but ACE inhibition is of particular interest because it has been shown to reduce all-cause mortality in patients with hypertension.[6]

Mechanisms by Which ACE Inhibition and ARBs Reduce IMT

Cacciatore et al[51] proposed a mechanism to show how treatment with ACE inhibitors can improve IMT. They conducted a study that included 36 patients newly diagnosed with mild hypertesion without existing CVD. The patients were randomized into 2 treatment groups, receiving either enalapril or zofenopril. The patients were followed for > 5 years with carotid duplex ultrasound for measuring IMT, and blood samples were drawn to check for endothelial progenitor cells (EPC), plasma nitrite and nitrate levels, and isoprostane levels. It has been hypothesized that EPCs migrate to dysfunctional endothelium to facilitate endothelial repair and that this function is depressed in patients with atherosclerosis.[52] Over time, patient EPCs increased and there was a significant inverse correlation between the number of circulating EPCs and IMT. Plasma nitrate levels increased in both groups and isoprostane levels decreased, signaling a decrease in oxidative stress.

Angiotensin receptor blockers are thought to decrease IMT by a similar mechanism, mainly reducing reactive oxygen and increasing NO.[53] A study on 100 patients showed treatment with candesartan decreased IMT progression while also increasing NO and reducing oxidative stress.[53] A separate study on 20 patients measured ARB effects on IMT markers, including superoxide dismutase and lipid peroxidase, in patients with hypertension. Each of these markers was reduced with ARB treatment when compared with diuretic therapy.[54]

Genetics may also play a role in IMT progression and response to treatment.[55–59] Bozec et al[59] studied the M235T polymorphism in the angiotensinogen gene, its effects on IMT, and response to treatment. The gene polymorphism under investigation has been correlated with increased angiotensinogen levels and increased prevalence of hyper-tension.[55–58] The study found that in previously untreated patients with hypertension, those who were homozygous for the T allele had a significantly greater reduction in IMT compared with patients who were homozygous for the MM allele, when treated for blood pressure correction. The TT allele could be an early biomarker for atherosclerosis and a predictor of IMT response to treatment.[59]

Clinical Trials Evaluating the Effects of ACE Inhibitors and ARBs on IMT

ACE Inhibition and IMT

Mayet et al[60] first reported that ACE inhibition reduces IMT in data from a small study on 13 patients. The patients enrolled had hypertension and were treated with ramipril and felodipine rescue therapy for 6 months. Rescue therapy was defined as continuing ramipril treatment, then adding felodipine to the regimen until the patient reached the target blood pressure of 140/90 mm Hg. A significant reduction in IMT was observed at the end of the intervention, and it was proposed that the effect was due to blood pressure reduction.[60]

In 1997, ACE inhibition with fosinopril sodium was compared with a modified-diet–only regimen for 12 months of treatment in patients with asymptomatic diabetic hypertension. Patients had their IMT measured at the beginning and end of the intervention. The results showed a 4.3% increase in IMT for those patients in the ACE inhibitor–treatment group and a 15.1% increase in IMT for the diet-only group.[61] Boutouyrie et al designed a double-blind study to compare 2 different treatment regimens for patients with essential hypertension. One patient group was given ACE inhibors and enalapril, and the other group received β-adrenoceptor antagonists and celiprolol. Both groups were treated for 9 months. Measurements of patient IMT were taken from the carotid and radial arteries. Each treatment group showed a similar reduction in carotid IMT, but radial IMT was more significantly reduced in patients treated with ACE inhibitors and enalapril than in those treated with β-andrenoceptor antagonists and celiprolol. The study suggested that a reduction in pulse pressure correlates with carotid IMT reduction but not with radial artery IMT reduction.[62,63] This is particularly notable because the carotid artery is an elastic artery and the radial artery is more muscular. The study also suggested that reducing local pulse pressure may have a more significant role in reducing IMT than a reduction in overall mean blood pressure.

A large, randomized, placebo-controlled trial on 617 patients with coronary, cerebrovascular, or peripheral vascular disease analyzed the effects of ramipril therapy on IMT changes. The study found no significant difference in IMT measurements after 4 years of treatment with an ACE inhibitor. The authors suggested that the decrease in mortality associated with ACE inhibitors was due to decreases in blood pressure and reduced endothelial dysfunction as opposed to reversing atherosclerosis.[64] When IMT progression was measured for effect of long-term ACE inhibitor (enalapril) therapy in patients with non–insulin-dependent diabetes mellitus, the results showed a significantly smaller progression of IMT thickening in the group treated with ACE inhibitors.[65]

The Plaque Hypertension Lipid-Lowering Italian Study (PHYLLIS) was a large multicenter trial comparing the effects of treatment with hydrocholothiazide (HCTZ) compared with fosinopril, both with and without pravastatin therapy, on IMT in patients with dyslipidemia and hypertension.[33] Study data showed that fosinopril was more effective than HCTZ therapy alone in reducing IMT. Data also showed that adding statin therapy improved IMT more than placebo[66]; however, the study did not show a difference between fosinopril therapy and treatment with fosinopril and pravastatin. The study concluded that fosinopril has a greater protective effect than HCTZ against atherosclerosis progression, independent of blood pressure. The Study to Evaluate Carotid Ultrasound Changes in Patients Treated With Ramipril and Vitamin E (SECURE) was a long-term (4.5 years), prospective, double-blind trial that compared the effects of ramipril treatment with vitamin E treatment on IMT in high-risk patients. Patients had diabetes and vascular disease plus ≥ 1 other risk factor for IMT progression. Study data revealed that treatment with ramipril reduced the progression of IMT in a dose-dependent fashion compared with vitamin E, which was not more effective than placebo.[67] The trial suggested that IMT reduction may be better achieved with adequate doses of ACE inhibitors. To date, SECURE has been the largest and longest study completed to evaluate the impact of treatment with ACE inhibitors on IMT.

Asselbers et al[68] conducted a double-blind, placebo- controlled study to evaluate the effect of fosinopril or pravastatin on urinary albumin excretion and IMT in patients with microalbuminuria (PREVEND IT). The study showed no significant change in patient IMT between the treatment groups. Fosinopril did lower urinary albumin excretion significantly after 3 months of therapy. The trial showed a significant increase in cardiovascular events if patient baseline IMT was > 1 mm, suggesting earlier therapeutic intervention aimed at reducing IMT may help to reduce later cardiovascular events.

A small, randomized, controlled trial conducted by Napoli et al[7] compared the effects of long-term treatment with a carboxylic ACE inhibitor (enalapril) or a sulfhydryl ACE inhibitor (zofenopril) on IMT in patients with mild hypertension. The results showed a significant reduction in IMT progression for patients treated with zofenopril compared with patients treated with enalapril. Patients in the zofenopril group also had less reduction in NO compared with patients treated with enalapril. The study revealed that different ACE inhibitors may have different effects on the thickness of the vascular wall.

ARBs and IMT

The mixed results gained from treating IMT with ACE inhibitors led to the investigation of ARB therapy and its effects on IMT. Angiotensin receptor blocker therapy has the advantage of reduced side effects, namely coughing, compared with ACE inhibitor therapy. The mode of action with ARB treatment is to directly block AT1 receptor activation, a more downstream component of the RAS compared with the role of ACE inhibition. A potential advantage of ARB use is that the AT2 receptor remains uninhibited.[69] Activation of the AT2 receptor is one of the steps shown to be involved in tissue repair following myocardial infarc tion and may promote arterial health by stimulating NO synthesis.[69]

The Losartan Vascular Regression Study (LAARS) was a double-blind, randomized, controlled trial investigating the effects of losartan compared with atenolol therapy on carotid IMT. In patients with mild-to-moderate hypertension, IMT was significantly reduced in both treatment groups. However, when looking at femoral artery IMT, the investigators did find more reduction in patients treated with losartan compared with atenolol.[70] In a follow-up study, Ariff et al[71] investigated the effects of candesartan compared with atenolol treatment on IMT in 88 patients with uncontrolled hypertension and end-organ damage. Study data showed that both treatment groups had a similar rate of IMT reduction; however, atenolol therapy was associated with inner carotid artery remodeling and a smaller reduction in left ventricular mass index than was losartan treatment. It has been shown that β-adrenergic receptor antagonism inhibits renin secretion, which could help explain the IMT regression with atenolol therapy.[72]

A small study by Uchiyama-Tanaka et al[73] compared the efficacy of treatment with ARB (losartan) compared with ACE inhibitor therapy (quinapril) in reducing IMT progression in 57 patients with mild-to-moderate hypertension. Patients in each treatment group had similar blood pressure improvements; however, the IMT of patients treated with quinapril was significantly reduced (10%) compared with those of patients in the losartan-treated group. The study suggested that ACE inhibitors are more effective at reducing IMT than are ARBs.

In another study, 75 previously untreated patients with moderate-to-severe hypertension were randomized and treated with either ramipril or telmisartan to lower blood pressure. If the blood pressure could not be controlled with a single drug, both were administered. Every patient group exhibited a reduction in IMT after the 6-month trial period. The telmisartan-treated group exhibited a significantly greater reduction in IMT than did patients in the ramipril treatment group. Combined therapy produced the greatest reduction in IMT.[74] The study suggested that increased inhibition of the RAS has an increased effect in improving IMT.

The Swedish Ibersartan Left Ventricular Hypertrophy Investigation Versus Atenolol (SILVHIA) study compared the effects of ARB (ibersartan) treatment with atenolol therapy on IMT in 108 patients with hypertension. The study showed that with similar blood pressure reductions, carotid IMT was reduced with ibersartan (not significantly from baseline), but significantly increased with atenolol when compared with baseline. A significant difference in blood pressure rates between the 2 treatment groups was also reported. Additionally, the study showed a difference in how vessels remodeled. Atenolol

use produced inward vessel remodeling, whereas losartan produced outward remodeling, which caused ibersartan-treated patients to show smaller reductions in lumen diameter than atenolol-treated patients.[75] The impact of ARB treatment on outward remodeling is attractive but has not been replicated in other studies.

The Multicenter Olmesartan Arterosclerosis Regression Evaluation (MORE) study included 165 patients with hyper-tension and common carotid artery plaques. To reduce IMT progression, patients were treated with either olmesartan or atenolol for 104 weeks. The study showed that both atenolol and olmesartan treatment significantly reduced IMT, but there was no significant difference between treatment groups. There was a difference, however, in plaque volume between the 2 treatment groups. Patients who were given olmesartan exhibited a significant reduction in large plaque volume from baseline, whereas patients who received atenolol did not.[76]

Sonoda et al[77] investigated the use of losartan, enalapril, or imidapril, compared with placebo, to reduce IMT in 50 Japanese patients with hypertension. The investigators found that IMT was significantly decreased with both the ARB and ACE inhibitor treatment compared with placebo, but there was no significant difference between the intervention groups, suggesting that treatment with ARBs is as effective as treatment with ACE inhibitors in reducing IMT.

In a small study of 35 patients by Mizuguchi et al,[78] patients with previously untreated hypertension were given telmisartan therapy for 12 months. Each newly treated patient had IMT monitoring at 1 month and 12 months following initiation of therapy. The treated group was compared with a placebo control group; IMT was measured at 1 month and 12 months for the control group as well. Results showed no significant differences between the control and telmisartan-treated groups. Table 1 summarizes the major studies conducted to control IMT progression with ARB and ACE inhibitor therapy.

Discussion

Overall, treatment with ACE inhibitors has been shown to reduce IMT progression. However, the differences in patient comorbidities, drug dosages, adequacy of blood pressure management, and choice of drug in the various conducted trials all likely contribute to a lack of cohesion in the literature. In particular, patients enrolled in the studies ranged from having mild hypertension, to severe hypertension, to end-organ damage. Possibly, treating IMT with ACE inhibitors and ARBs is most effective only in certain groups (ie, patients at moderate or highest risk for cardiovascular events) or in patients with relatively high blood pressure. Intima-media thickness has been shown to improve with several classes of antihypertensive medications, including β-blockers, ACE inhibitors, ARBs, and calcium channel blockers. Furthermore, the use of a placebo may not be warranted in treatment studies of patients with documented hypertension. Future studies will likely compare patient groups with participants who all have effective blood pressure management.

To clarify the data, therapeutic dosing strategies and individual medication regimens need to be further investigated. The SECURE trial showed that increasing the dose of ACE inhibitor

increased the reduction in IMT.[79] The trials we have reviewed in this article used dosing strategies aimed at controlling blood pressure. It could be possible that increased dosing above standard blood pressure control levels could provide an increased benefit to the arterial wall.

The type of ACE inhibitor may also play a role in reducing IMT.[7] Napoli et al[7] postulated that the wide variation in ACE inhibitor chemical structure may account for some of the varying results in reducing IMT. Our work has postulated that sulfhydryl ACE inhibitors improve IMT profiles more effectively than carboxylic ACE inhibitors due to improved oxygen stress profiles.[80]

Chymase activity must also be considered when evaluating efficacy of treatment with ACE inhibitors. Chymase is a serine protease that independently converts angiotensin I to angiotensin II.[81] It is released from mast cells in response to an inflammatory stimulus, which is often present in pathologic processes.[82] Pathology related to chymase activity typically occurs locally due to its association with mast cells.[82] More work is needed to assess the importance of chymase activity and its effects on IMT progression. Adding an ARB to ACE inhibitor therapy could be of benefit by blocking AT1 receptors, which are activated by chymase-generated angiotensin II.

When comparing the effectiveness of ACE inhibitor and ARB treatment on IMT, there is no clear benefit of one class or the other, but there remains a suggestion that because they both function at different sites, there could be synergy of effect on the arterial wall with dual-agent therapy. However, in the absence of clear benefit to patients, ACE inhibitors will probably remain the first line of treatment for IMT progression due to its benefit of reducing all-cause mortality.[83]

Conclusion

Unfortunately, we know that only about half of patients with hypertension have the condition adequately controlled.[52,81] Blood pressure control remains an unmet need, and until improved, the impact of IMT may remain best used as a biomarker used to to call the patient's and physician's attention to at-risk behaviors and necessary medical conditions.

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Table 1

Major Studies[a] Identifying the Relationship of ACE Inhibitors, ARBs, and IMT

Investigators	Population	Subjects, N	Comparator Agents	Outcome Measure
ACE Inhibitor Trials				
Boutouyrie et al[62]	Essential hypertension	98	Enalapril vs celiprolol	Enalapril ↓ IMT
MacMahon et al[64]	Coronary artery disease	617	Ramipril vs no treatment	No difference in IMT
Hosomi et al[65]	Non–insulin-dependent DM	98	Enalapril vs placebo	Enalapril ↓ IMT
Zanchetti et al[66]	Dyslipidemia and hypertension	508	Fosinopril vs HCTZ	Fosinopril ↓ IMT progression
Lonn et al[67]	High-risk patients[b]	732	Ramipril vs placebo	Ramipril ↓ IMT
Asselbergs et al[68]	Microalbuminuria	642	Fosinopril vs placebo	No difference in IMT
ARB Trials				
Ludwig et al[70]	Mild-to-moderate hypertension	280	Losartan vs atenolol	No difference in IMT
Ariff et al[71]	Uncontrolled hypertension with end-organ damage	88	Candesartan vs atenolol	No difference in IMT
Uchiyama-Tanaka et al[73]	Moderate hypertention	57	Losartan vs atenolol	Losartan ↓ IMT
Petrovic et al[74]	Moderate-to-severe hypertension	75	Telmisartan vs ramipril	Telmisartan ↓ IMT Telmisartan with ramipril ↓ IMT vs telmisartan monotherapy
Mortsell et al[75]	Hypertension	108	Ibesartan vs atenolol	Ibesartan ↓ IMT
Stumpe et al[76]	Hypertension with common carotid plaque	165	Olmesartan vs atenolol	No difference in IMT Olmesartan ↓ large plaque volume
Sonoda et al[77]	Hypertension	50	Losartan vs enalapril or Imidapril vs placebo	Losartan and enalapril or imidapril ↓ IMT

Abbreviations: ACE, angiotensin-converting enzyme: ARB, angiotensin receptor blocker; DM, diabetes mellitus; HCTZ, hydrochlorothiazide; IMT, intima-media thickness.

[a] Major study: ≥ 50 subjects.

[b] Diabetes, vascular disease, plus 1 other risk factor.