

Mechanisms of cardiovascular risk reduction with ramipril: insights from HOPE and HOPE substudies

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Angiotensin converting enzyme (ACE) inhibitors decrease angiotensin formation, prevent breakdown of bradykinin, and may also act on other peptides of the renin-angiotensin system. Thus, these agents have many effects that can potentially protect the coronary and peripheral vasculature. Which of these “theoretical” mechanisms account for the clinical benefit observed in The Heart Outcomes Prevention Evaluation (HOPE) trial? While the answer to this question is complex and cannot be fully answered, several potential mechanisms have been explored *within* HOPE and its substudies. These studies

demonstrate that ramipril has potent effects on atherosclerosis progression and plaque stabilization as well as on myocardial structure and function. Ramipril also improves glucose metabolism. These effects are dose-dependent but largely blood pressure independent.

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Introduction

The Heart Outcomes Prevention Evaluation (HOPE)^[1] study showed significant benefits in preventing a range of cardiovascular (CV) outcomes in high-risk patients with vascular disease and/or diabetes and additional risk factor(s) and without heart failure or systolic dysfunction who were treated with the high tissue affinity angiotensin-converting enzyme (ACE) inhibitor ramipril (10 mg · day⁻¹). After an average 4.5 years of therapy, the patients randomised to ramipril had a 22% reduction in the risk of sustaining a major vascular event (CV death, myocardial infarction [MI], or stroke) compared to those randomised to placebo (all patients also received conventional therapy with other cardiac and vascular protective interventions based on accepted patterns of practice). There were reduced risks for MI (relative risk reduction [RRR] 20%, 95% confidence interval (CI), 10%–30%; $P < 0.001$); CV death (RRR 26%, 95% CI, 13%–36%; $P < 0.001$); stroke (RRR 32%, 95% CI, 16%–44%; $P < 0.001$), heart failure (RRR 23%; 95% CI, 13%–33%, $P < 0.001$), revascularization (RRR 15%, 95% CI, 16%–23%; $P = 0.002$), and worsening angina (RRR 11%, 95% CI, 4%–18%; $P = 0.004$). Other adverse outcomes including all-cause death (RRR 16%, 95% CI, 15%–25%, $P = 0.005$), diabetic nephropathy (RRR 16%, 95% CI, 1%–29%; $P = 0.036$); and the development of new

diabetes (RRR 34%, 95% CI, 15%–49%; $P < 0.001$) were also prevented.

Experimental models and mechanistic studies in humans suggest that ACE inhibitors exert numerous cardiac and vascular protective actions, which are a consequence of (a) decreased angiotensin (Ang) II formation, (b) prevention of the breakdown of bradykinin and, possibly, (c) modulating the action of other Ang peptides (Table 1)^[2]. Identifying which of these putative mechanisms account for the clinical benefit observed in the HOPE is complex and not easily ascertained. Several mechanisms have been explored *within* the HOPE trial through specific analyses and focused substudies and may be particularly relevant.

Blood pressure lowering

The importance of blood pressure (BP) lowering as a mechanism contributing to the significant clinical benefits observed in the HOPE trial has been controversial and much debated. Several lines of evidence suggest that in the high-risk population studied, comprising patients with a high prevalence of CV disease (87%), coronary heart disease (80%), diabetes (38%), and other risk factors, the ACE inhibitor ramipril confers substantial benefits that are unlikely to be fully explained by BP lowering. The mean initial BP in the HOPE study patients was 139/79 mm Hg and the observed BP lowering was modest (3.3/1.4 mm Hg reduction). The magnitude of benefit attained with ramipril was much greater than expected from the degree of BP

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Table 1 Beneficial effects of ACE inhibitors in atherosclerotic cardiovascular diseases

Blood Pressure Lowering	Vascular Protection
Cardiac Protection	Direct antiatherogenic
Decrease in preload and afterload	Enhanced endogenous fibrinolysis
Decrease in left ventricular mass	Inhibition of platelet aggregation
Improved myocardial remodeling	Antiproliferative and antimigratory for smooth muscles
Decrease in sympathetic stimulation	Antimigratory for mononuclear cells
Reduction in reperfusion injury	Decreased collagen matrix formation
Metabolic Effects	Improvement in endothelial function
Lipid neutral	Antioxidant
Improved glucose metabolism	Anti-inflammatory
	Protection from plaque rupture
	Improved arterial compliance and tone

lowering observed, as estimated from earlier epidemiological studies and clinical trials as well as from an analysis of the placebo arm *within* HOPE^[3]. Indeed, based on such analyses, a 3.3 mm Hg lowering in systolic BP would be expected to reduce the risk of MI by 5% and of stroke by 10%–15%. By contrast, in HOPE the RRR for MI was 20% and for stroke 32%. Furthermore, the reduction in risk attained with ramipril did not change significantly after statistical adjustments for time-dependent changes in systolic and in diastolic BP. Finally, treatment benefits were also seen in the normotensive population within HOPE, comprising patients with baseline BP below the median of 138/80 mm Hg, and importantly, these benefits were independent of, and additive to, those attained from other BP-lowering therapies, including beta-blockers, diuretics, and calcium channel blockers^[3].

Effects on atherosclerosis: Insights from the SECURE study

The Study to Evaluate Carotid Ultrasound changes in patients treated with Ramipril and vitamin E (SECURE), a substudy of the HOPE trial, randomised 732 patients in a 3 × 2 factorial design to treatment with a daily dose of ramipril 2.5 mg or 10 mg or placebo and to vitamin E 400 IU . day⁻¹ or placebo^[4]. The anatomic extent of atherosclerosis was evaluated at baseline and thereafter in follow-up by serial quantitative B-mode ultrasound examinations of the extracranial carotid arteries. Quantitative B-mode ultrasonography has been demonstrated to be a valid measure of anatomic extent of atherosclerosis and is increasingly used in clinical trials that test the effects of various interventions on the progression of atherosclerotic vascular disease^[5]. The background for the SECURE trial is provided by a wealth of experimental data demonstrating vascular protective properties of ACE inhibitors and by several animal models of experimental atherosclerosis that have suggested a possible direct antiatherogenic effect of ACE inhibitors independent of BP lowering^[6–8].

The SECURE study participants were similar to the HOPE study population. They were 55 years of age or older

with vascular disease or diabetes and at least one additional CV risk factor and did not have heart failure or low left ventricular (LV) ejection fraction. The average follow-up was 4.5 years. The main study outcome was the annualised progression slope of the mean maximum intima-media thickness (IMT) derived from measurements of the near and far walls of the common carotid, the bifurcation, and the internal carotid arteries (Fig. 1). The ultrasound measurements were highly reproducible and, by including bifurcation and internal carotid artery segments, provided a comprehensive evaluation of atherosclerosis in the extracranial carotid arteries, superior to that used in other studies, which have focused only on the common carotid artery (Table 2)^[9].

Patients treated with ramipril had significantly lower atherosclerosis progression rates. The progression rate of the mean maximum IMT was 0.0217 mm . year⁻¹ in the placebo group, 0.0180 mm . year⁻¹ in the ramipril 2.5-mg . day⁻¹ group, and 0.0137 mm . year⁻¹ in the ramipril 10-mg . day⁻¹ group ($P = 0.033$ for the overall effect of ramipril) (Fig. 2). Although the absolute difference in atherosclerosis progression rates between ramipril and placebo-treated patients is small, the relative reduction in mean maximum IMT was 37% for ramipril 10 mg . day⁻¹ versus placebo, which is quite considerable and similar to the 32% reduction in the risk for stroke observed in the HOPE trial^[10]. The effect was dose-dependent, with maximum benefit in patients receiving 10 mg ramipril daily and a trend towards benefit in patients receiving 2.5 mg ramipril daily. The majority of study patients were receiving various other effective drugs, including aspirin (84%), lipid-lowering agents (34% at baseline and 50% at study end), β -blockers (43%), diuretics (9%) nitrates (32%), and calcium channel blockers (43%). The effect of ramipril on atherosclerosis was independent of these interventions. Most study participants were normotensive with a mean baseline BP of 132/76 mm Hg. Ramipril had only a modest BP-lowering effect in this largely normotensive population. Furthermore, the benefits of treatment in retarding the anatomic progression of atherosclerosis remained statistically significant after adjusting for a history of hypertension, baseline BP, and BP changes over the duration of the study. Therefore, similar to the HOPE analysis, the SECURE study suggests that the benefit noted

Table 2 Randomized placebo-controlled trials evaluating the effect of ACE inhibitors on the anatomic progression of atherosclerosis

Trial	Sample Size	Patients	ACE Inhibitor (Daily Dose)	Followup (yrs)	Atherosclerosis Assessment	Results
QUIET ^[11]	477	CAD	Quinapril 20 mg	3	QCA	Overall neutral effect of treatment; decreased atherosclerosis progression with quinapril for patients with baseline LDL-C >3.2 mmol/L; improved endothelial function in the TREND ^[12] substudy of QUIET with quinapril 40 mg . day ⁻¹
SCAT ^[13]	460	CAD	Enalapril 10 mg bid	4	QCA	Neutral effect of treatment
PART-2 ^[14]	617	CAD, CeVD, or PAD	Ramipril 5–10 mg	4	Carotid IMT (CCF; 2 segments/patient)	Neutral effect of treatment
SECURE ^[4]	732	High risk CAD, prior stroke, PAD or diabetes with additional risk factor(s)	Ramipril 2.5 mg/10 mg	4	Carotid IMT (aggregate of 12 segments/patient)	37% reduction in the annualised slope of the mean maximum IMT; dose dependent benefit of treatment; significant treatment effect after adjusting for BP changes and other predictors of IMT progression
Hosomi <i>et al.</i> ^[15]	98	Type 2 diabetes	Enalapril 10 mg	2	Carotid IMT (CCA near and far wall; 4 segments/patient)	49% reduction in the annualised IMT slope; significant treatment effect after adjusting for other predictors of IMT progression

QUIET=Quinapril Ischemic Event Trial; SCAT=Simvastatin/Enalapril Atherosclerosis Trial; PART-2=Prevention of Atherosclerosis with Ramipril Trial; SECURE=Study to Evaluate Carotid Ultrasound changes with Ramipril and vitamin E; TREND=Trials on Reversing Endothelial Dysfunction; CAD=coronary artery disease; QCA=quantitative coronary angiography; CeVD=cerebrovascular disease; PAD=peripheral arterial disease; IMT=intima-media thickness; CCA=common carotid artery; CCF=common carotid far wall.

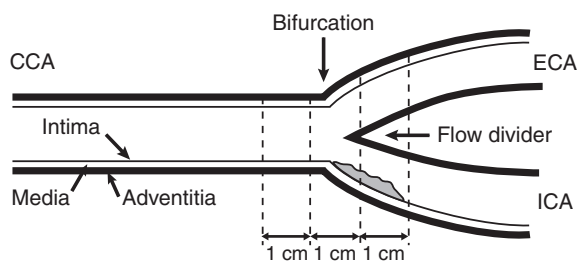


Figure 1 Quantitative B-mode carotid ultrasound methods used in the SECURE trial. The primary study outcome was the annualised progression slope of the mean segment maximum intima-media thickness measurements of the near and far walls of the right and left common carotid arteries (CCA), bifurcation, and internal carotid artery (ICA) segments (12 segments/ patient). ECA=external carotid artery.

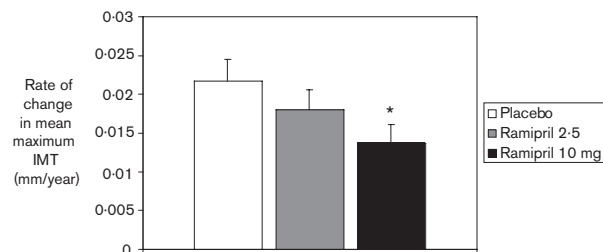


Figure 2 Effect of ramipril on the annualised slope of the mean maximum carotid intima-media thickness (IMT) in the SECURE trial. The mean duration of follow-up was 4.5 years. * $P = 0.028$ for ramipril 10 mg . day⁻¹ vs. placebo.

on atherosclerosis progression is not fully explained by BP lowering, is additive to other interventions, and may, indeed, be related to direct vascular protective effects of ramipril.

A number of other recent trials have also evaluated the effects of ACE inhibitors on atherosclerotic progression^[11–15]. These trials differ in their choice of study participants, the methods used for evaluating atherosclerosis

progression, and the choice of ACE inhibitor and regimen used, as well as the duration of therapy and follow-up (Table 2). Such differences may explain the inconsistent results of these studies. As summarised in Table 2, some studies found important reductions in atherosclerosis progression rates in patients treated with ACE inhibitors, while other studies failed to demonstrate this effect.

In spite of the overall inconsistent results of the trials evaluating the effect of ACE inhibition on the anatomic progression of atherosclerosis, it appears that a direct effect on atherosclerosis was an important mechanism of benefit in the HOPE study. In both the large parent HOPE trial and

in the SECURE substudy, a direct beneficial effect of ramipril was noted in a largely normotensive population. This benefit was largely independent of BP lowering, it was independent of and additive to other drugs, and, as suggested in SECURE, it was dose-dependent. The concordance of the results on atherosclerosis in SECURE and on clinical events in HOPE noted in similar patients suggests that, indeed, direct effects on atherosclerosis and plaque stabilization were major mechanisms accounting for the clinical benefits attained with ramipril.

Increased urinary albumin excretion is a strong independent risk factor for CV events in diabetic and nondiabetic individuals and is considered a marker of endothelial dysfunction and underlying vascular disease^[16]. Indirect evidence of a vascular protective action of ramipril in HOPE is also provided by the reduced risk of developing microalbuminuria and clinical proteinuria in study participants with and without diabetes treated with ramipril^[17,18].

The role of inflammation

Recent scientific advances have established a fundamental role for inflammation in mediating all stages of atherosclerosis, from initiation through disease progression and, ultimately, to plaque rupture and ensuing thrombotic complications leading to acute clinical events^[19]. Ang II activates inflammatory processes in the arterial wall by augmenting the release of inflammatory mediators from smooth muscle and endothelial cells and from activated macrophages directly and via production of reactive oxygen species^[20]. Bradykinin augments local production of nitric oxide, which has anti-inflammatory properties mediated through the interference with the nuclear factor kappa B (NF- κ B) transcriptional control pathway^[20]. ACE inhibitors may, therefore, decrease vessel wall inflammation by affecting both Ang II and bradykinin pathways.

Inflammatory markers, such as high-sensitivity C-reactive protein (hsCRP), fibrinogen, soluble intercellular adhesion molecule-1 (sICAM-1), and interleukin (IL)-6, were measured from baseline blood samples obtained in 3182 HOPE study participants. In unadjusted analysis using the lowest third as the referent group, the highest thirds of hsCRP, fibrinogen, sICAM and IL-6 significantly predicted CV risk. After adjusting for major atherosclerotic risk factors, the highest thirds of hsCRP (hazard ratio versus lowest third, 1.24, 95% CI, 1.02–1.52), fibrinogen (hazard ratio 1.40, 95% CI, 1.17–1.69), and sICAM-1 concentration (hazard ratio 1.46, 95% CI, 1.21–1.77) remained independently associated with the risk of major CV events, whereas IL-6 did not^[21]. The beneficial effect of ramipril was greater in the highest thirds of hsCRP, fibrinogen, and sICAM-1 concentrations compared with the lowest thirds^[21]. This finding suggests a possible relationship between increased “inflammatory status” and vascular protection conferred by ACE inhibition. Further analyses of the effects of ramipril on hsCRP levels and on other inflammatory markers are ongoing in a subset of HOPE

study participants in whom serial blood samples were collected. The question of ACE inhibitor action on soluble inflammatory markers is also under investigation in other ongoing studies.

The prevention of diabetes and improved glucose metabolism

Diabetes is a strong independent risk factor for CV diseases^[22]. More recently, the degree of hyperglycemia in people with diabetes and insulin resistance and dysglycemia in nondiabetic individuals have also been linked to increased risk for atherosclerosis and vascular events^[22,23]. ACE inhibitors may improve these metabolic abnormalities. For example, several older studies suggest that ACE inhibitors increase insulin-mediated disposal of glucose and therefore insulin sensitivity in individuals without and with diabetes^[24,25]. Other mechanisms by which ACE inhibitors may improve glucose metabolism include prevention of hypokalemia with resultant improved β -cell insulin secretory response to glucose; reduced Ang II mediated vasoconstriction in the pancreas; reduced insulin resistance in skeletal muscles, an effect shown to be related to bradykinin-mediated nitric oxide production; and decreased insulin resistance in hepatocytes and fat cells^[26].

The HOPE trial showed a significant reduction in the risk of developing new self-reported diabetes in patients treated with ramipril. New diabetes was reported by 102 participants [3.6%] in the ramipril group and 155 [5.4%] in the placebo group (RRR 44%, 95% CI, 15%–49%; $P < 0.001$)^[26]. Similar results were reported in other large clinical trials of ACE inhibitors or Ang-receptor blockers^[27,28]. The reduction in new diabetes observed in HOPE is supported by a metabolic substudy of the trial in which fasting plasma glucose, insulin, and proinsulin were measured at baseline and after 2 years in over 400 participants without diabetes. Fasting glucose increased more in patients in the placebo group, 0.41 mmol/L, than in those in the ramipril group, 0.25 mmol/L ($P = 0.029$)^[29]. There were also trends toward decrease in insulin and proinsulin levels in ramipril-treated patients, although these did not reach statistical significance. Among the diabetic individuals in HOPE, those in the ramipril arm of the study had improved glycemic control, as evidenced by lower HgA_{1c} levels^[17]. These favourable metabolic actions likely also contributed to the CV benefits attained with ramipril.

Effects on myocardial structure and function

Increased left ventricular (LV) mass has been identified as an independent risk factor for coronary heart disease and is associated with increased cardiac mortality and morbidity^[30,31]. While LV hypertrophy occurs primarily in hypertensive individuals, the Framingham Heart Study suggested an association between LV mass and CV

Table 3 Effects of ramipril on left ventricular mass and function (echocardiographic substudy). Changes in study-end versus baseline echocardiographic measurements

	Placebo (n = 151)	Ramipril 2.5 mg . day ⁻¹ (n = 149)	Ramipril 10 mg . day ⁻¹ (n = 146)	P for trend
Changes in left ventricular mass index (g/m ²)	+3.9 ± 25	+4.2 ± 22	-2.0 ± 27	0.02
Changes in left ventricular end-diastolic volume (mL)	+4.2 ± 31	-0.4 ± 33	-5.9 ± 35	0.01
Changes in left ventricular end-systolic volume (mL)	+5.3 ± 20	+2.9 ± 18	-1.9 ± 19	0.01
Changes in left ventricular ejection fraction (%)	-2.0 ± 9	-1.5 ± 9	-0.1 ± 9	0.06
Changes in wall motion score	+0.05 ± 0.14	+0.028 ± 0.13	+0.018 ± 0.10	0.06

mortality in the general population^[31]. ACE inhibitors have been consistently shown to be effective in reducing LV mass in animal models and in hypertensive subjects^[32,33]. Similarly, ACE inhibitors have been shown to reduce cardiac volumes and improve ventricular function in patients with coronary heart disease^[34]. The beneficial effect of ACE inhibitor therapy on LV mass and LV remodeling is mediated through hemodynamic effects of these agents but also through load independent mechanisms related to reduced Ang II-mediated myocyte hypertrophy, decreased aldosterone formation and bradykinin-mediated actions^[32,35-37].

In the HOPE study, electrocardiograms were recorded at baseline and at study end. Significantly fewer patients in the ramipril group (8.1%) had development or persistence of LV hypertrophy by electrocardiographic criteria than in the placebo group (9.8%) and more patients in the ramipril group (91.9%) had regression or prevention of electrocardiographic LV hypertrophy than in the placebo group (90.2%) ($P = 0.007$)^[38]. This effect of ramipril on LV hypertrophy was independent of BP changes and, importantly, patients who had regression or prevention of electrocardiographic LV hypertrophy had a lower risk of major vascular events compared with those who had development or persistence of electrocardiographic LV hypertrophy.

In an echocardiographic substudy of HOPE, LV mass and function was measured in 446 patients randomised to placebo or a daily dose of ramipril 2.5 mg or 10 mg and followed for 4 years^[39]. Ramipril significantly reduced LV mass and LV volumes with trends toward improved LV ejection fraction and wall motion score. These effects were dose-dependent and could not be explained by BP changes alone (Table 3)^[39]. These findings demonstrate that long-term ACE inhibitor therapy has a beneficial dose-dependent effect on LV remodeling and function in high-risk patients with vascular disease without hypertension or with well-controlled BP and without heart failure or LV dysfunction.

Conclusions

The action of ACE inhibitors in cardiac and vascular disease is complex and multi-faceted. While BP lowering is a key part of the mechanism of benefit of ACE inhibitors, this

alone is inadequate in explaining the multiple clinical benefits of these agents. Several important mechanisms of action of ramipril were explored within the HOPE trial and its substudies and are likely to have contributed to the large clinical benefit observed in this trial. These include a decrease in atherosclerosis, an improvement in vascular function, a direct impact in preventing myocardial hypertrophy, and a reduction in glucose levels and the potential to prevent diabetes. Additional mechanisms may also be involved and require further exploration.

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