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Scientific Update™

Major issues for the cardiovascular high-risk patient: Rationale and evidence provided by HOPE

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The Heart Outcomes Prevention Evaluation (HOPE) trial[1] showed that the angiotensin-converting enzyme (ACE) inhibitor ramipril significantly reduced a wide range of cardiovascular events in a high risk population with normal cardiac function. The stimulus for this trial evolved from findings in the heart failure trials SAVE[2] and SOLVD[3] where, in addition to reductions in heart failure mortality and morbidity, a decreased incidence of acute coronary events was observed. Furthermore, the plasma levels of ACE activity and variations of the human ACE gene have been associated with the risk of myocardial infarction (MI).[4]

HOPE recruited 9541 patients at high risk of vascular events in 267 centres (129 centres in Canada), randomized them to ramipril 10 mg daily or placebo, and followed their clinical course for 4-6 years. After 3 years treatment with ramipril, cardiovascular mortality was reduced 26% (Table 1).

This treatment benefit was achieved in patients with normal left ventricular function. Stroke (fatal CVA, incapacitating stroke, disabling and nondisabling stroke) was reduced 32% (CI, 0.56-0.84, p<0.001) in a normotensive population. Furthermore, the benefits of ramipril were achieved whether or not patients were taking beta-blocking agents, lipid-lowering medication, or ASA. The need for coronary and peripheral revascularization was reduced by ramipril. Diabetic patients had a 24% reduction in mortality, and non-diabetics had a 34% reduction in the development of new diabetes whilst taking ramipril. The magnitude of the clinical impact of HOPE is substantial and best expressed by considering the number of reduced events (Table 2).

Further analysis of data from the HOPE trial has provided some insight into the mechanisms of the extensive and substantial treatment benefit from ramipril in the management of patients at high risk of complications from vascular disease.

Are the results of HOPE due to a reduction in blood pressure?

When the results of HOPE were initially presented there was concern that the reduction in events resulted entirely from the hypotensive effect of ramipril. Further analysis has confirmed initial observations, showing that the benefits of ramipril were several-fold greater than would be observed from the observed fall in blood pressure. The changes in blood pressure during the study are shown in Table 3

The same reduction of cardiovascular death, stroke, and myocardial infarction was achieved for the lower three quartiles of systolic pressure. However, for patients with systolic

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Table 1: Summary of the HOPE Trial

Patients: > 55 years old, evidence of vascular disease or diabetes plus one cardiovascular risk factor, no heart failure, or known low LVEF
Medication: Ramipril 10 mg daily or placebo
Follow-up: 5 years

Results

	Ramipril %	Placebo %	Risk reduction %	P value
Primary end-point MI, CVA, CV death	14.0	17.8	22	<0.001
Cardiovascular mortality	6.1	8.1	26	<0.001
MI	9.9	12.3	20	<0.001
Revascularization procedure	16.0	18.3	12	<0.002
Stroke	3.4	4.9	32	<0.001

blood pressure >150 mm Hg, event rates were reduced more than for those with lower pressures.

The increased benefit of treatment with ramipril in the hypertensive population is not surprising. Analysis of hypertension treatment trials has demonstrated a linear relationship between blood pressure lowering and reduction of stroke, MI, and death rates. A 10-15 mm Hg reduction of an elevated systolic blood pressure results in a 40% reduction in stroke rate and a 15% reduction of MI.The reduction of both stroke and MI in the HOPE trial greatly exceeded the benefits predicted from the small 3.3 mm Hg reduction of systolic pressure (Table 4).

In HOPE the reduction in event rates was similar whether or not the baseline blood pressure was elevated. SBP > 140 or DBP > 90: RRR 0.74 (CI 0.65-0.83). SBP < 140, DBP <90: RRR 0.85 (CI, 0.78-0.93). Furthermore, the benefits of ramipril were observed with or without anti-hypertensive medications such as beta-adrenergic blocking agents, calcium channel antagonists, or diuretics.

Table 2: Clinical impact of HOPE Trial

For 1000 patients treated with ramipril over 3 years there will be a reduction of:

Death	18
MI	16
CVA	9
Revascularization	26
Heart failure	26
Cardiac arrest	5
Complication of diabetes	12
New onset of diabetes	15
Total events reduced	**128**

Table 3: Change in blood pressure during HOPE

	Baseline	1 year	2 years	End of study
Systolic				
Ramipril	138.50	-5.51	-3.32	-2.19
Placebo	138.85	-1.69	0.0	0.38
Diastolic				
Ramipril	78.9	-2.73	-2.66	-3.14
Placebo	79.0	-0.56	-1.01	-2.09

Thus, the benefits of ramipril in patients at high risk of vascular complications appear to be independent of the reduction of blood pressure, with events reduced independent of baseline blood pressure. The reduction of events in the HOPE trial is disproportionately greater than that observed in the hypertensive trials, especially for the reduction of MI, when the magnitude of risk reduction is similar to that for stroke. Although it is very likely that the benefits of ramipril were achieved independently from any change in blood pressure, there are limitations in this interpretation. HOPE was not a blood pressure trial. Consequently, there were a limited number of duplicate pressure measurements. Recordings were not made with random zero recorders, and digit preference is evident from the individual observations. In addition, all recordings were office measurements which may not reflect real blood pressure changes.

Despite these minor limitations, the analysis shows that the reduction in event rates by ramipril was additive to the benefits of other medications, regardless of their class and independent of the blood pressure. If antihypertensive medication is needed, ramipril would be expected to provide benefits in addition to those predicted from its blood pressure lowering effect alone.

Is the dose of ramipril important?

The benefits of ramipril were achieved in the HOPE trial using a target dose of 10 mg daily. The SECURE trial[5] investigated whether progression of atherosclerosis could be reduced with ramipril 2.5 mg and 10 mg. The patients

Table 4: Predicted and observed reduction of event rates resulting from the 3.3 mm Hg reduction of systolic pressure in HOPE

	Predicted	HOPE
Stroke	15%	31%
MI	< 5%	20%

Table 5: Change in carotid arterial IMT slope (mm/year): SECURE Trial[5]

	Placebo	Ramipril 2.5mg	Ramipril 10mg
Max IMT slope	0.022	0.018	0.014
		p=0.028	

Overall ramipril effect p=0.033

enrolled in the study had similar entry criteria as those in HOPE: 35% were hypertensive and 40% were on cholesterol-lowering medication. The intimal-medial thickness (IMT) of the carotid artery was measured by B mode ultra-sound, and the results expressed as the change in IMT in mm / year.

A significantly greater reduction in the rate of atherosclerosis progression was achieved at the higher dose of ramipril, despite similar blood pressure reductions at both doses.

Ramipril 10 mg daily also achieved greater reductions in left ventricular mass than 2.5 mg daily (change in LV mass (g): placebo + 3.97, ramipril 2.5 mg + 4.15, ramipril 10 mg – 2.02). This reduction in LV mass was achieved mainly by a reduction of left ventricular wall thickness with smaller changes in left ventricular chamber size.

These studies suggest that the vasculo-protective and cardio-protective effects of ramipril observed in the HOPE trial are best achieved with the target dose of 10 mg daily. Patients should be started on lower doses (ramipril 2.5-5 mg daily), and the dose increased to the target dose of 10 mg daily over 1-2 weeks.

Can other ACE inhibitors provide the same benefits observed in HOPE?

Are the observations of the HOPE trial a class effect for all ACE inhibitors? There will be no clear answer to this question until clinical trials such as the Prevention of Events with Angiotensin-Converting Enzyme (PEACE)[6] and the EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA)[7] with other ACE inhibitors are completed in similar patients at high risk of vascular events with normal left ventricular function. Yet, the stimulus for the HOPE trial was the observation that enalapril and captopril reduced the incidence of MI in patients with heart failure. It is likely, therefore, that other ACE inhibitors will provide some vascular protective benefit. However, only captopril, enalapril, ramipril, lisinopril and trandolapril have been shown to reduce (recurrent) MI in either trials of heart failure (SOLVD,[3] SAVE[2]) or following MI (AIR,[8] TRACE[6]). A pooled meta-analysis[9] of SOLVD, AIRE, SAVE, and TRACE has shown that ACE

Table 6: Economic implications of the use of ramipril in patients at high risk of vascular events (costs in 1999 Canadian $)

	Ramipril	Placebo	
Hospital costs	$2430	$2994	
Procedures	$1970	$2323	
Medication	$4302	$3270	
Total	$8702	$8587	p ns
3% discount	$8019	$7915	p ns

inhibitors reduce MI by 21% (CI, 11-29%, p=0.001), hospitalization for unstable angina by 20% (CI, 9-29%, p=0.001), and the need for revascularization by 24% (6-39%, p=0.01).

Only ramipril has been shown to reduce vascular events in patients without left ventricular dysfunction and in high risk patients with diabetes (HOPE). It is unknown if ACE inhibitors other than ramipril will have the same magnitude of benefit as observed in the HOPE study. Furthermore, the dose of other ACE inhibitors required to achieve the optimal benefit is unknown. Thus, evidence-based practice would recommend that patients with normal ventricular function at high risk of vascular events should be started on ramipril 10 mg daily until clinical trials show that other ACE inhibitors give the same or better protection. For patients already taking an ACE inhibitor with proven vascular protection, it is reasonable to continue treatment, although the dose should be at the level shown to be effective in clinical trials.

Is ramipril cost-effective in patients at high risk of vascular complications?

A cost-effective analysis of the use of ramipril 10 mg daily for 4½ years in patients at high risk of vascular complications as defined in the HOPE study has shown that the benefits of ramipril can be achieved with no increase in net cost. (Table 6). This analysis by Andre Lamy used a modular case costing system and assumed a medication cost of $28.50 / month. The reduction of events (MI, CVA, congestive heart failure, cardiac arrest, ventricular arrhythmias, and TIA), and procedures (coronary bypass surgery, percutaneous coronary intervention, carotid endarterectomy and peripheral vascular surgery) shown by the HOPE study were included in the model.

Ramipril reduced the cost of diagnostic tests, revascularization, and non-study medication. Thus, ramipril in patients at high risk of vascular events provides an important improvement in clinical outcome, is cost neutral, and is a dominant strategy for the management of this large group of patients.

Implications for the management of hypertension

The control of hypertension is aimed at target organ protection and the prevention of stroke, MI, and renal damage. In the HOPE study, target organ protection was achieved independent of the level of blood pressure. However, patients with arterial pressures in the upper quartile of blood pressure had greater benefit than those in the lower three quartiles. In a high-risk diabetic population in the UKPDS study,[10] tight blood pressure control resulted in a decrease in stroke and renal failure, yet no reduction in coronary events. Although the benefits were achieved by both a beta-adrenergic blocker and the ACE-inhibitor captopril, almost one-third of the patients required three drugs to achieve adequate control. The HOT study[11] also demonstrated that combination therapy is necessary to achieve a target diastolic BP ≤ 80 mm Hg, which was associated with the lowest incidence of cardiovascular events in the diabetic subpopulation.

The FACET trial,[12] in patients with hypertension and diabetes, showed that although amlodipine and fosinopril were equally effective for blood pressure control over the 3.5 years of follow-up, patients receiving fosinopril had a lower risk of fatal and non-fatal cardiovascular events compared to those receiving amlodipine. The ABCD trial[13] compared enalapril with nisoldipine in the management of diabetic patients with hypertension. The ACE-inhibitor enalapril was also associated with a lower risk of both fatal and non-fatal MI. Whether the results of the ABCD and FACET trials are due to an increased vascular risk from calcium-channel blockers or to the vascular-protective effects of ACE-inhibitors is not known.

The need for tight blood pressure control in high risk patients, especially those with diabetes, is evident from several trials, most of which demonstrate that several agents are necessary to achieve target blood pressure. The HOPE trial suggests that a proven ACE inhibitor such as ramipril should be included as one of the anti-hypertensive agents to maximize target organ protection in patients at high risk of cardiovascular complications.

Conclusions

The HOPE trial has shown that the ACE inhibitor ramipril prevented events from cardiovascular disease. There was a reduction of a variety of events in a broad group of high risk patients without left ventricular dysfunction. The benefits of treatment with ramipril in this group of patients are not explained by blood pressure reduction, and it is likely that the therapeutic effect is due to an improvement in endothelial function.

As most patients in HOPE were taking a variety of medications including ASA and beta-adrenergic blocking agents, ramipril provided added value to the current treatment. The potential target population is enormous, including all patients with established cardiovascular disease, and patients with diabetes and at least one risk factor for vascular disease.

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