SMH ST. MICHAEL'S HOSPITAL Cardiology
UNIVERSITY OF TORONTO
A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO
Scientific Update™

Emerging therapeutic role of the angiotensin-converting enzyme inhibitors: Implications of the HOPE Study

Canadian Cardiovascular Society Meeting

Quebec City, Quebec, October 19-23, 1999

Reported and discussed by:
GORDON MOE, MD

Hypertension, atherosclerosis, and diabetes are the key risk factors for the development of cardiovascular disorders. These conditions damage blood vessels and the major organs such as the heart and kidneys, resulting in endothelial dysfunction, vascular and cardiac remodeling, and hypertrophy. These pathological processes ultimately lead to either acute myocardial infarction (MI), or progressive left ventricular dysfunction, culminating in heart failure. The renin-angiotensin-aldosterone system (RAAS) has been implicated in a significant number of steps of this progression. Angiotensin-converting enzyme (ACE) inhibition is the most established therapeutic strategy to intervene the RAAS, and the ACE inhibitors (ACEIs) have become the cornerstone of the therapy of heart failure and the secondary prevention of MI. Results of the recently reported Heart Outcomes Prevention Evaluation (HOPE) Study have extended the therapeutic role of ACEIs to patients at high risk for cardiovascular events in the absence of heart failure or MIs.

Angiotensin-converting enzyme inhibitors (ACEIs) are widely used in the treatment of asymptomatic patients with systemic hypertension. On the opposite end of the spectrum of disease progression, ACEIs prolong survival in patients with chronic heart failure (CHF)[1,2] and these agents have become a "cornerstone" of pharmacologic therapy in patients with symptomatic CHF.

In 1987, investigators from the Scandinavian countries first reported in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) that enalapril, an ACEI, improved 6-month mortality rate by 40% in patients with *severe* CHF.[1] This was a landmark study as it was the first trial that demonstrated the use of ACEIs for secondary prevention. Subsequently, the beneficial effect of enalapril on survival was demonstrated in the Study of Left Ventricular Dysfunction (SOLVD) study, published in 1991, on patients with *moderate* CHF.[2] More recently, the clinical effectiveness of ACEIs for secondary prevention in patients who have experienced an MI has also been demonstrated.[3,4] In the Survival and Ventricular Enlargement (SAVE) trial published in 1992, the ACEI captopril was shown to improve survival in patients post-MI, who were asymptomatic but had a reduced left ventricular ejection fraction of ≤ 40%.[3] Subsequently, in the Acute Infarction Ramipril Efficacy (AIRE) study published in 1993, another ACEI ramipril was found to reduce mortality by 27% in patients post-MI with clinical evidence of heart failure, but not necessarily documented left ventricular systolic dysfunction.[4] In the AIRE extension follow-up study (AIREX) published in 1997, the beneficial effects of ramipril appeared to be maintained at 3 years after the AIRE study was closed (Figure 1).[5]

In the Studies of Left Ventricular Dysfunction (SOLVD) trial, the patients with reduced left ventricular (LV) ejection fraction, besides having improved survival, also experienced

St. Michael's Hospital, 30 Bond St., Suite 9-004, Queen Wing, Toronto, Ontario M5B 1W8 Fax: (416) 864-5330

The topics presented in *Cardiology Scientific Update* are independently determined and the content authored exclusively by physician-members of the Division of Cardiology, St. Michael's Hospital. *Cardiology Scientific Update* is made possible by unrestricted funding from the publisher, Snell Medical Communication Inc., which has received educational grants from the pharmaceutical industry for the distribution of this publication.

Table 1: Effect of ramipril on primary outcome

	Ramipril n=4645	Placebo n=4652	RR	95% CI	p
MI, stroke, CV death	13.9%	17.5%	0.78	0.70-0.86	0.000002
CV death	6.0%	8.0%	0.75	0.64-0.87	0.0002
MI	9.8%	12.0%	0.80	0.71-0.91	0.0005
Stroke	3.3%	4.8%	0.68	0.56-0.85	0.0002
Non-CV death	4.3%	4.2%	1.00	0.82-1.35	0.98
All-cause mortality	10.3%	12.2%	0.83	0.74-0.94	0.0035

a reduction in MIs and unstable angina with ACEI therapy.[6] In the Survival and Ventricular Enlargement (SAVE) trial, patients post-MI also had reduced incidence of recurrent MIs and cardiac revascularizations with the use of ACEI.[7] Indeed, in patients with coronary artery disease, ACEI has been shown to improve endothelial function.[8] These data therefore suggest that ACEI exerts anti-ischemic effects and may modify the process of atherosclerosis.

Vitamin E has antioxidant and antiplatelet effects. Observational studies suggest that increased consumption of vitamin E and other antioxidants in the form of dietary supplements is associated with a lower risk of cardiovascular events.[9,10] However, definitive data from large-scaled randomized-controlled trials addressing hard clinical endpoints are still lacking. The encouraging results of the ACEI studies and the uncertainty of the benefit of vitamin E formed in part the rationale of the Heart Outcomes Prevention Evaluation (HOPE) study that is discussed below.

The HOPE study

The HOPE study was a Canada-initiated international study conducted in 19 countries to assess the effect of ACEI and antioxidant therapy in patients at high risk for vascular events. The principal objective was to examine the effect of the ACEI ramipril (up to 10 mg/day) versus placebo in reducing cardiovascular (CV) events and/or the antioxidant vitamin E (400 IU/day) versus placebo on heart disease, stroke, and cancer in patients at high risk of CV events. Therefore, the study population was not targeted as a disease population, but rather as a high risk of disease population. The primary endpoint of HOPE was a cluster endpoint of CV death, MI, and stroke. The secondary outcomes included the need for revascularization, unstable angina, CHF hospitalization, diabetes complications, and cancers. A simple double-blind, 2x2 factorial design of ramipril versus placebo and vitamin E versus placebo with very wide entry criteria was used. The inclusion criteria included age >55; any evidence of vascular disease, i.e. coronary artery disease (CAD), stroke and peripheral vascular disease (PVD); and diabetes mellitus plus one additional coronary risk factor. The principal exclusion criteria were history of heart failure or known reduction in LV ejection fraction, ongoing use of ACEI or vitamin E, and acute ischemic event within 4 weeks. Nine thousand five hundred and forty-one patients were followed for 4.6 years. The study was powered to detect a relative risk reduction (RRR) ≥12% overall and RRR ≥15-25% in the key prospectively defined subgroups in the both the primary and secondary outcomes. Two hundred and sixty seven hospitals from 19 countries participated in the study.

The study began recruitment in January 1994. The last patient was recruited in May 1995. The study was terminated early by the study's independent Data and Safety Monitoring Board on March 23, 1999, because of clear benefit demonstrated in the ramipril arm. The investigators were notified

Table 2: Effect of ramipril on heart failure events

	Ramipril n=4645	Placebo n=4652	RR	95% CI	p
All CHF	7.4%	9.4%	0.78	0.67-0.90	0.0005
CHF hospitalizations	3.2%	9.5%	0.84	0.72-1.10	0.13
CV death and all CHF	11.9%	15.3%	0.77	0.69-0.86	0.000003
CV death and CHF hospitalization	8.4%	10.7%	0.77	0.68-0.88	0.0001

Table 3: Diabetes complications in the total population and the diabetes subgroup

	Overall population			Diabetes only		
	Ramipril (%)	Placebo (%)	RR	Ramipril (%)	Placebo (%)	RR
All diabetic complications	6.4	7.7	0.83*	14.9	17.6	0.83
Overt nephropathy/dialysis	3.2	4.2	0.74**	6.9	8.6	0.78*
Laser therapy (retinopathy)	3.7	4.0	0.92	9.4	10.8	0.88
New microalbuminuria	20.2	22.5	0.90*	33.0	37.0	0.90
New diabetes	3.8	5.5	0.69**	–	–	––

* p<0.05, **p<0.01

on April 17, 1999. Closeout visits were completed by mid-August. Vital statistics were ascertained on 99.3% of the patients. The data presented in this report represent data accumulated up to August 25, 1999.

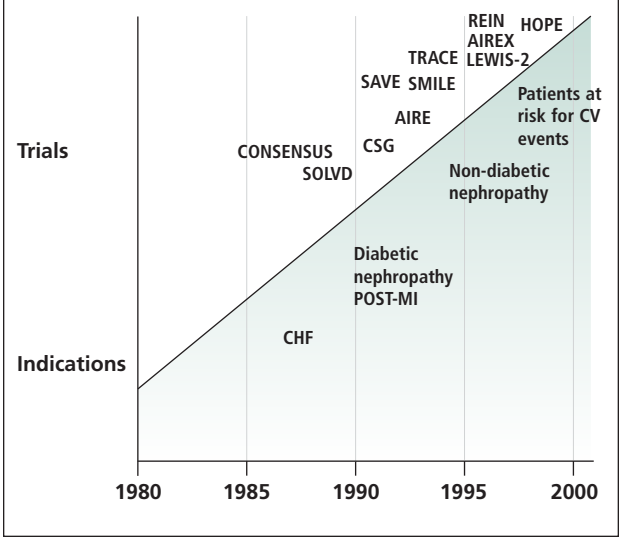
Results

The results of the vitamin E arm of the study indicate no effect on the primary and secondary cardiovascular outcomes. The primary outcome, a composite endpoint of CV death, MI, and stroke, was 16 and 15.4% for the vitamin E and placebo arms respectively, relative risk (RR)=1.03, 95% confidence interval (CI), 0.94-1.15, p=0.42. However, there was a suggestion of a significant reduction in the hospitalization and deaths from cancer, RR=0.83, 95% CI, 0.78-0.99, p=0.048, and the incidence of all cancers, RR=0.84, 95% CI, 0.71-0.99, p=0.034.

The key positive finding of HOPE is the significant reduction of cardiovascular events by the ACEI ramipril. Data for the primary outcome and its components are shown in Table 1. There was a significant reduction in the primary outcome as well as individual components of this composite primary outcome. Total mortality was also significantly reduced by 17%. Of the pre-specified secondary outcomes of unstable angina, heart failure hospitalizations, revascularization, hospitalization and deaths from cancer and all cancers, there was a significant reduction in heart failure hospitalization, RR=0.84, CI, 0.64-0.97, p=0.0257 and revascularization, RR=0.86, CI, 0.77-0.95, p=0.0025. Total frequency of heart failure was significantly reduced, as was the open label use of ACEI for CHF, RR=0.72, p=0.0017, the composite endpoint of CV death and all CHF, or CV death and CHF hospitalization (Table 2). The reduction in primary endpoint was maintained in the 4676 patients (2339 ramipril, 2337 placebo) with known normal LV ejection fraction, RR=0.73, CI=0.63-0.84, p=0.00002. A similar trend was observed in each component of the endpoint, suggesting that the positive findings of the whole group were not due to contamination with patients with impaired LV function. Finally, ramipril also reduced the total rate of revascularization, 16% in ramipril, 18.4% in placebo, RR=0.85, p=0.0013.

The HOPE study contains insightful information regarding the impact of ACEI therapy on patients with diabetes. In the 3578 patients with diabetes (1808 ramipril, 1770 placebo), a significant reduction in the primary outcome composite events, RR=0.76, p=0.0007 and total mortality, RR=0.79, p=0.0024, was observed. Importantly, as shown in Table 3, diabetes-related events such as overt nephropathy, use of laser for retinopathy, and new microalbuminuria, were significantly reduced by ramipril in both diabetic, as well as nondiabetic patients. Finally, the beneficial effect of ramipril on the primary outcome was present regardless of patients' age, gender, the presence or absence of hypertension, CAD, cerebrovascular disease, PVD, microalbuminuria, as well as the concomitant use of ß-blockers, lipid-lowering agents, and aspirin.

Figure 1: Emerging therapeutic role of the ACEIs



It is interesting to note that treatment with ramipril was associated with only a modest 2.17 mm Hg reduction of systolic and 3.13 mm Hg reduction of diastolic arterial pressure at the end of study. Based on previous trials where a 10-15 mm Hg reduction in systolic pressure was associated with a 40% reduction in stroke and 15% reduction in MI, the modest reduction of blood pressure in HOPE would be translated to a 13% reduction in stroke and a 5% reduction in MI. The 32% reduction in stroke and the 21% reduction in MI's observed in HOPE would therefore suggest that the beneficial effects of ramipril was not mediated only by its blood pressure-lowering effect.

Summary

In summary, the HOPE study demonstrates that in patients at risk for vascular disease, the ACEI ramipril prevents CV deaths, strokes and MI, the need for CHF hospitalization and revascularization, as well as the development of diabetes and diabetes complications and nephropathy. The data of ramipril on primary outcome translate essentially to treating only 6 patients for 4.5 years to reduce one composite cardiovascular event. The findings of a lack of an effect of vitamin E on cardiovascular events is important and the possible impact on the development of new cancers offers hope after the neutral results reported by trials such as the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC study)[10] and GISSI Prevention Study. To address these issues further, an extension of HOPE, the HOPE-TOO (Heart Outcomes Prevention Evaluation-The Ongoing Outcome) study has been proposed. The plan is to continue two-year follow up of the HOPE patients, with continued blinding for vitamin E and assessment of outcomes with ramipril unblinded.

Data from the HOPE study has now extended the therapeutic role of ACEI from patients with CHF and post-MI to patients without CHF and recent MI, but at *high* risk for vascular events (Figure 1). Aside from the reduction of CV events, the beneficial effect of ramipril on overt nephropathy and microalbuminuria is also noteworthy. This favorable effect of ramipril is consistent with earlier findings from the Collaborative Study Group (CSG) demonstrating that captopril protected against deterioration in renal function in insulin-dependent diabetic nephropathy,[11] as well as the recently reported Ramipril Efficacy in Nephropathy (REIN) study showing ramipril conferred renoprotection in non-diabetic nephropathies with or without nephrotic proteinuria.[12,13]

Other studies with ACE inhibitors

The ongoing Prevention of Events with Angiotensin-Converting Enzyme inhibition (PEACE) study, as well as the EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA),[14] will hopefully address the therapeutic role of ACEI in patients at even lower risk for CV events than those in the HOPE study. The PEACE study will randomize over 8000 patients to the ACEI trandolopril or placebo. A preliminary assessment of the baseline demographics of PEACE that includes age, incidence of diabetes, cerebrovascular disease, and PVD, and the use of coronary procedures, suggests that patients in the PEACE study are a lower risk population than in the HOPE study. At this point, patients who are at high risk for CV events and who fit into the inclusion criteria of the HOPE study would likely benefit from treatment with an ACEI such as ramipril.

References

1. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;316:1429-35.
2. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fraction and congestive heart failure. *N Engl J Med* 1991;325:293-302.
3. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the survival and ventricular enlargement trial (the SAVE investigators). *N Engl J Med* 1992;327: 669-77.
4. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity in survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;342:82108.
5. Hall AS, Murray GD, Ball SG. Follow-up study of patients randomly allocated ramipril or placebo for heart failure after acute myocardial infarction: AIRE Extension (AIREX) Study. *Lancet* 1997;349:1493-97.
6. Yusuf S, Pepine CJ, Garces C, et al. Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. *Lancet* 1992;340:1173-8.
7. Rutherford JD, Pfeffer MA, Moye LA, et al. Effects of captopril on ischemic evetns after myocardial infarction. Results of the survival and ventricular enlargement tiral. SAVE investigators. *Circulation* 1994;4:1731-8.
8. Mancini GBJ, Henry GC, Macaya C, et al. Angiotensin-converting enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary artery disease. *Circulation* 1996;94:258-65.
9. Hoffman RM, Garewal HS. Antioxidants and the prevention of coronary artery disease. *Arch Intern Med* 1995;155:241-6.
10. Hennekens CH, Gaziano JM. Antioxidants and heart disease: epidemiology and clinical evidence. *Clin Cardiol* 1993;4:I10-3.
11. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med* 1993; 329:1456-62.
12. Ruggenenti P, Perna A, Gherardi G, Gaspari F, Benini R, Remuzzi G, on behalf of Gruppo Italiano di Studi epidemiologici in Nefrologia (GISEN). Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. *Lancet* 1998;352:1252-56.
13. Ruggenenti P, Perna A, Gherardi G, et al. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet* 1999;354:359-64.
14. Fox KM, Henderson JR, Bertrand ME, Ferrari R, Remme WJ, Simoons ML. The European trial on reduction of cardiac events with perindopril in stable coronary artery disease (EUROPA). *Eur Heart J* 1998;19:J52-5.